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The American Heart Journal

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Original Communications

AURICULAR PAROXYSMAL TACHYCARDIA*

THE EFFECT OF EPINEPHRINE, QUININE, QUINIDINE, ATROPINE AND DIGITALIS

HAROLD L. OTTO, M.D., AND HARRY GOLD, M.D.
NEW YORK, N. Y.

THE clinical manifestations of auricular paroxysmal tachycardia have been fully described. Its characteristically abrupt onset and cessation have made it very difficult, however, to obtain dependable data concerning the effects of drugs on this rhythm. Quinine, quinidine, and digitalis have been frequently employed in patients with paroxysmal tachycardia. The results obtained have been extremely variable, some reporting these drugs to be without influence on the attacks; others having found them of considerable value. Lewis[1] and others reported that atropine did not influence attacks of auricular paroxysmal tachycardia; Galli[2] found that paroxysms were provoked by atropine; while others have recommended the use of atropine in the treatment of attacks. Detailed studies of single cases of auricular paroxysmal tachycardia yield important data but have led in some cases to erroneous generalizations concerning the behavior of this condition because there are a number of factors, as we shall show, that may contribute to the production of this rhythm and are, in all probability, of varying importance in different cases. Observations have been made under widely varying conditions with different doses of the drugs. Furthermore, authors have, in general, made little distinction between the efficiency of these drugs in preventing the occurrence of attacks and stopping paroxysms already in progress. These factors must be considered, in the interpretation of seemingly contradictory results with drugs obtained by different observers, in order to yield a better understanding of the mechanism of auricular paroxysmal tachycardia.

*From the Third (New York University) Medical Division and Adult Cardiac Clinic, Bellevue Hospital and Department of Pharmacology, Cornell University Medical College.

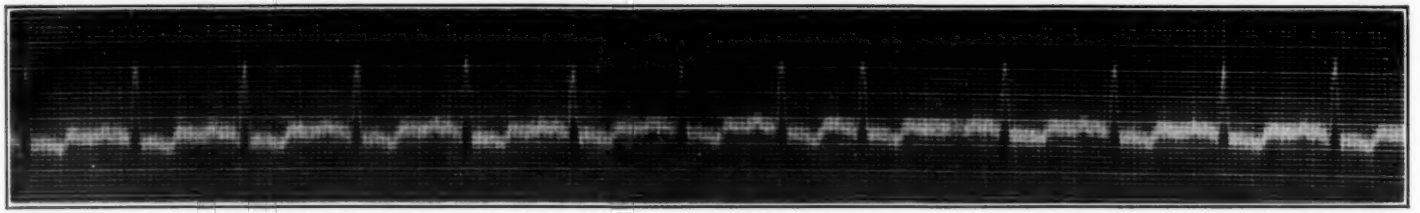

Fig. 1.—Showing electrocardiogram (Lead I) taken in the interval between paroxysms. The sinus rhythm is interrupted by occasional auricular premature contractions.

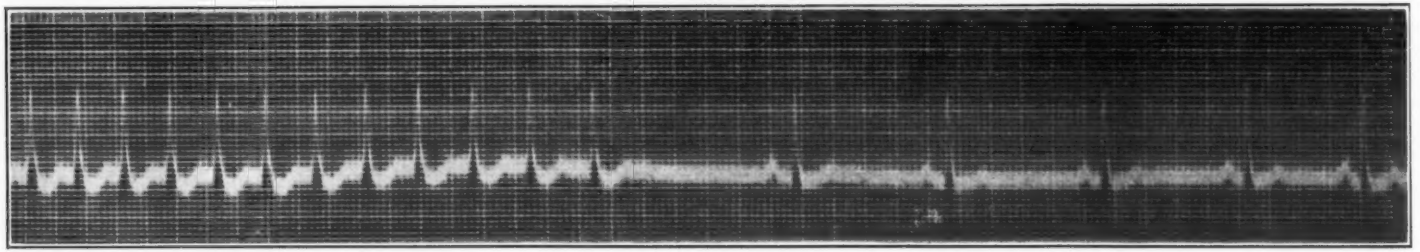

Fig. 2.—Showing electrocardiogram (Lead II) of spontaneous attack of auricular paroxysmal tachycardia and cessation of paroxysm with resumption of sinus rhythm.

The present report is based on a study of the effects of quinine, quinidine, digitalis, atropine, and epinephrine in a case of auricular paroxysmal tachycardia.*

The study was facilitated by the accidental finding that a paroxysm could be precipitated by epinephrine when the patient was not under the influence of any other drug. Part of the study was carried out with the patient under control in the hospital, and part while the patient attended the clinic. Frequent electrocardiograms and clinical records were taken before, during, and after the administration of the drugs. It was found impossible to carry out all the experiments in the order in which they were planned or as exhaustively as was desired. It is considered, however, that the observations so far as they could be carried are of sufficient interest to report.

CLINICAL HISTORY AND PROCEDURE

Spontaneous Tachycardia.—The patient, a woman, twenty-three years old, was admitted to the hospital with symptoms of subacute rheumatic fever. She improved and was discharged thirteen days later. The cardiac diagnosis was enlarged heart with mitral stenosis and insufficiency of rheumatic origin, sinus arrhythmia, auricular premature contractions, and very mild signs of myocardial insufficiency. Two days later she was readmitted to the hospital after two attacks which she described as follows: After a few minutes, during which she was conscious of an impending attack, vision became blurred, there was ringing in the ears, shortness of breath, and a feeling as if the heart were fluttering, then brief loss of consciousness. These paroxysms lasted about five hours. Upon examination the heart was regular with a rate of 192 per minute and remained thus unchanged by position, by pressure on the neck in the region of both vagi† or by pressure on the eyeballs during three hours of continuous observation. Then while preparing for an intravenous injection of quinine, the rate suddenly dropped to 72 per minute with a regular sinus rhythm and remained thus until the patient was discharged four days later. The electrocardiograms taken during the attack showed auricular paroxysmal tachycardia. (See Fig. 2.)

Spontaneous Tachycardia—Quinine.—After a period of several weeks, during which the patient had had several paroxysms, she was readmitted to the hospital during a similar attack. This time she received an intravenous injection of 0.33 gram (5 grains) of quinine dihydrochloride, one hour after the onset of the attack. The electro-

*To simplify expression, "Auricular paroxysmal tachycardia" will be frequently referred to as attack or paroxysm.

†Pressure on both sides of the neck over the carotid sheath will be referred to as vagal pressure following the designation by Czermak, although Hering has recently presented evidence to show that the procedure results in a reflex originating in the region of the carotid rather than in direct vagus stimulation, and Erben has advanced the view that compression of the jugular veins by this procedure raises the intracranial venous pressure and thereby stimulates the vagus.

cardiogram before the injection showed a heart rate of 204 per minute and the same rate one, five, twenty, and sixty minutes, respectively, after the injection. Spontaneous resumption of the normal sinus rhythm and rate of 78 per minute occurred about five hours later. Having had no attacks in the succeeding nine days she was again discharged with a supply of quinidine sulphate to be taken in doses of 0.2 gram twice daily by mouth.

Spontaneous Tachycardia—Quinidine.—Six weeks later the patient again entered the hospital with the history of freedom from attacks for the first four weeks, but frequent attacks in the last two weeks during which she was without quinidine. On admission the heart rate was 76 per minute and the rhythm regular. The administration of quinidine sulphate by mouth in doses of 0.2 gram twice daily was resumed. The heart rate and rhythm remained unchanged during the next four days.

Quinidine—Exercise—Epinephrine.—At the end of this time exercise to the point of breathlessness caused the heart rate to rise from 78 to 140 per minute with return to 78 in five minutes. Later that day a dose of 1 c.c. of a 1:1000 solution of epinephrine was given subcutaneously and the dose repeated in fifteen minutes. The electrocardiograms showed no change in the rhythm of the heart as the result of the epinephrine injections. The rate rose as high as 110 per minute ten minutes after the second injection. Up to this time the patient had been receiving quinidine daily.

Exercise—Epinephrine Tachycardia—Quinine.—The quinidine was discontinued for seven days and then the exercise test and the epinephrine in two doses were repeated. Exercise produced the same effect as on the previous occasion. Thirty minutes after the first dose and fifteen minutes after the second injection of epinephrine the heart rate rose to 135 per minute, was regular and unaffected by deep breathing or vagal pressure. Four minutes later or nineteen minutes after the second injection, the rate suddenly rose to 216 per minute and remained thus unaltered by vagal pressure or change in position or deep breathing. Twenty minutes later 0.33 gram (5 grains) of quinine dihydrochloride was given intravenously. The electrocardiogram before the injection showed an auricular tachycardia with a rate of 210 per minute. Immediately after the injection the rate was 196 per minute, after ten minutes 180, after forty minutes 185, after seventy minutes 190, and after two hours 190. The attack ended abruptly about six hours after the onset. The patient was again discharged after six days with a normal rate and sinus rhythm.

Quinidine—Epinephrine.—Fourteen weeks elapsed during which time the patient took 0.2 gram of quinidine sulphate twice daily by

mouth. There were no attacks during this period. She was then readmitted to the hospital for further study. On admission the heart rate was 81 per minute with a regular sinus rhythm. The following day a 1:1000 solution of epinephrine was again injected subcutaneously in 5 doses of 1 c.c. each at intervals of fifteen minutes. The sinus rhythm persisted though the rate increased to 125 per minute and the sinus arrhythmia which the patient often presented became considerably accentuated. This, therefore, was the second occasion on which epinephrine during the exhibition of quinidine failed to precipitate a paroxysm.

Epinephrine Tachycardia—Quinine.—After five days without quinidine, epinephrine solution 1:1000 was again injected subcutaneously in two doses of 1 c.c. each with an interval of fifteen minutes. Seventeen minutes after the second dose, there was an abrupt onset of tachycardia with a rate of 220 per minute which was unaffected by posture or vagal pressure. There was dizziness, marked dyspnea, and precordial pain. Twenty minutes later quinine dihydrochloride in twice the previous dose (0.66 gram) was injected slowly intravenously. Immediately following the injection the patient volunteered that the precordial pain had disappeared though dizziness and dyspnea persisted. Before the injection of the quinine the electrocardiogram showed a tachycardia with a rate of 220 per minute. Immediately following the injection it was 210 per minute; after five minutes 204; after fifteen, twenty, and thirty minutes, respectively, 186; after sixty minutes 190; after two hours 196; after three hours 204. The tachycardia ended abruptly about five hours following its onset.

Atropine—Epinephrine.—Two days later atropine sulphate was given hypodermically in two doses of 2 milligrams each with an interval of twenty minutes. Within one hour there was dilatation of the pupils and dryness of the mouth. The electrocardiograms showed a regular sinus rhythm with a rate of 78 per minute before the injection. After the drug was given the rhythm remained unchanged but the rate increased. In thirty-five minutes after the last injection the rate was 96, after sixty-five minutes 108, after eighty minutes 96. Epinephrine in solution of 1:1000 was then injected subcutaneously in a dose of 1 c.c. and the dose repeated fifteen minutes later. Electrocardiograms taken at intervals of five minutes beginning immediately after the second injection showed the following rates: 106, 114, 116, 126, 132, 132, 132, 130. The sinus rhythm remained unchanged.

Epinephrine Tachycardia.—Two days later epinephrine in solution of 1:1000 was again administered subcutaneously in two doses of 1 c.c. each with an interval of fifteen minutes. Seventeen minutes after the second injection a tachycardia set in with a rate of 200 per minute. The attack ended abruptly thirty-seven minutes later.

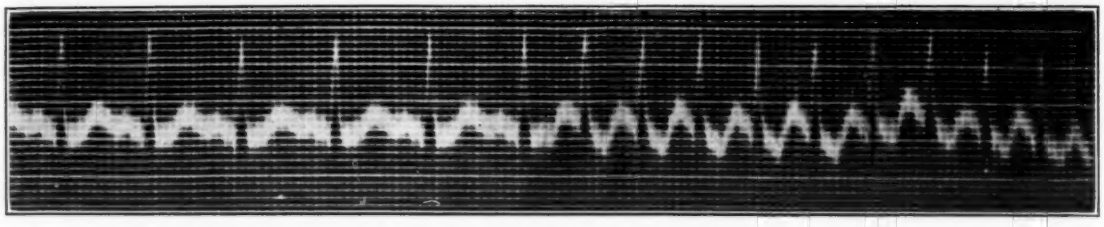

Fig. 3.—Showing electrocardiogram (Lead II) of the onset of auricular paroxysmal tachycardia after epinephrine.

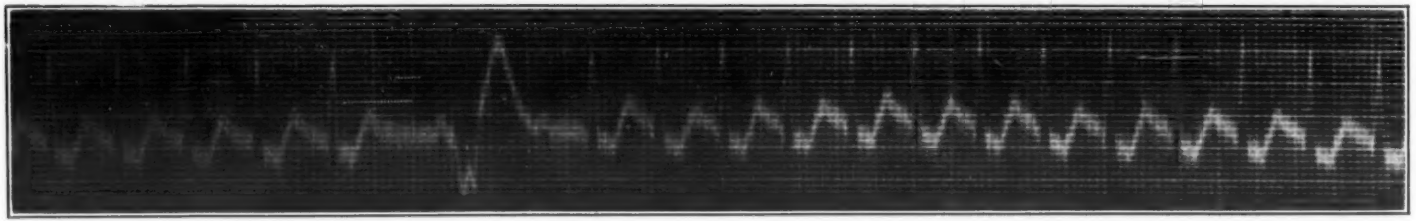

Fig. 4.—Showing electrocardiogram (Lead I) of auricular paroxysmal tachycardia induced by epinephrine in the digitalized heart. The rate is slower than that in the undigitalized heart and rhythm is interrupted by ventricular premature contractions.

Digitalis—Atropine—Epinephrine.—The following day the patient was digitalized with a tincture of digitalis, 0.15 cat unit per pound of body weight (total 22 c.c.) being given by mouth in a single dose. Eight hours later the normal sinus rhythm prevailed as before the digitalis, the T-wave in Lead II had become inverted, and the heart rate had dropped from 76 to 68 per minute. At this time a dose of 2 milligrams of atropine sulphate was given hypodermically and repeated in twenty minutes. One hour later the pupils were dilated and the mouth was dry. The sinus rhythm remained unchanged, but the rate rose to 104 per minute. Epinephrine was then injected in two doses as on all previous occasions with the result that the rate rose to 126 per minute but no change in the rhythm occurred.

Digitalis—Epinephrine Tachycardia—Atropine.—After twenty-four hours (sufficient for the disappearance of the atropine effect on the heart) epinephrine in the dose given above again precipitated an attack of paroxysmal tachycardia seven minutes following the second injection. The attack was interrupted by frequent ventricular premature contractions. One hour after the appearance of the tachycardia the subcutaneous injection of 2 milligrams of atropine sulphate resulted in frequent interruptions of the tachycardia by short periods of normal sinus rhythm. About four hours after the onset of the attack normal sinus rhythm reappeared.

COMMENT

Epinephrine.—Auricular paroxysmal tachycardia was induced by epinephrine in a patient predisposed to spontaneous attacks. Under the effect of epinephrine the heart rate slowly rose from 70 per minute with marked sinus arrhythmia to 136 per minute with a very regular rhythm, then suddenly altered its rhythm to that of auricular paroxysmal tachycardia with a rate of 216 per minute. This was repeated at four different times throughout the study with practically the same results. The tachycardia so induced lasted longer than the generally recognized duration of the systemic action of epinephrine and was indistinguishable from the spontaneous attacks in point of symptoms, rate, duration, electrocardiographic tracings, behavior toward change of position or vagal pressure and response to quinine. The inference is therefore justifiable that the focus and the mechanism of the spontaneous and induced attacks in this patient are identical, hence, the observations on the induced paroxysms are, in all probability, applicable to those occurring spontaneously. Whether or not the rise in the heart rate or the blood pressure caused by epinephrine contributed to the production of the paroxysm cannot be said. These factors alone were not sufficient to induce an attack as seen by the exercise experiments in which the heart rate rose to 140 per minute and the blood pressure rose from 110 systolic,

80 diastolic, to 170 systolic, 90 diastolic. The effect on the heart rate was greater than, and that on the blood pressure the same as, the effect produced by epinephrine. In two instances in which atropine had been given to paralyze the vagus endings, epinephrine failed to produce an attack. It appears therefore that in this case, both direct sympathetic as well as indirect vagus stimulation by epinephrine were necessary to induce auricular paroxysmal tachycardia.*

Quinine.—Quinine was given intravenously during one spontaneous paroxysm and two attacks induced by epinephrine. Both 5 and 10 grain doses were without effect other than to slow somewhat the rate of the tachycardia. The sudden disappearance of the precordial pain following the quinine administration was of some interest, but there was no opportunity to repeat this observation. It may be mentioned in parenthesis that the errors to which the therapeutic investigation of this arrhythmia is exposed were pointedly illustrated by the instance referred to above, in which a paroxysm suddenly came to a close as the quinine was about to be administered.

Quinidine.—Under the effects of quinidine spontaneous attacks failed to occur for a period of five weeks at one time and fourteen weeks at another time. That quinidine exerted a protective action is strongly suggested by the fact that attacks were frequent before its administration, were absent during the periods when the drug was being taken, and reappeared as the effects of the drug began to disappear. More positive evidence in this direction was obtained by the action of epinephrine during the administration of quinidine. This was tested twice. Whereas without quinidine epinephrine never failed to induce a paroxysm, during the use of quinidine, a paroxysm could not be induced by epinephrine either in the usual or in two and one-half times the usual dose.

Atropine and Vagal Influence.—The administration of atropine in doses sufficient to paralyze the vagus on two occasions produced no change in the sinus rhythm but accelerated the heart rate. Epinephrine given before the atropine induced a paroxysm. Under the influence of atropine epinephrine failed to induce an attack, and after the effect of atropine had worn off epinephrine again induced a paroxysm. The same results were obtained on repetition. As stated above, Galli[2] found that atropine induced attacks in his patient predisposed to spontaneous paroxysms. The changes in the heart rate after the atropine were not given in sufficient detail to make it pos-

*Since there is some evidence that the vagus plays a part in the production of auricular paroxysmal tachycardia, we shall refer in this paper to the effect of large doses of atropine as equivalent to the effect of paralysis of the vagus endings. Hatcher and Weiss[3] have shown that the vagus and sympathetic nerves are far less distinct pharmacologically and physiologically than anatomically and that the sympathetic nerve possesses specific afferent fibers or functions that are paralyzed by atropine. What applies to the afferent functions of the sympathetic in all probability applies to the efferent also, hence, it is conceivable that epinephrine may induce a paroxysm by action on specific nerve fibers of the sympathetic which may be paralyzed by atropine. Such an hypothesis awaits further evidence.

sible to determine the exact significance of his results. He did observe a marked slowing of the heart rate after 1 milligram of atropine prior to the onset of the paroxysm in some cases, indicating vagus stimulation. The doses he employed were not sufficient to cause complete paralysis of the vagus endings.[4] It is possible, therefore, that atropine induced a paroxysm in his case by vagus stimulation, hence, his observations are in harmony with ours, namely, that paralysis of the vagus by atropine not only failed to induce an attack but prevented the production of an attack by epinephrine.

Digitalis.—After a full dose of digitalis there was slight slowing of the heart rate but no change in the sinus rhythm. When vagus control was removed by atropine during full digitalization, epinephrine failed to induce a paroxysm. In the presence of an active vagus epinephrine produced an attack in the digitalized heart as in the normal heart. The only differences observed in the paroxysm of the digitalized heart were that the rate was slower, 162 as against 200 to 222 per minute, and further that the tachycardia was frequently interrupted by premature ventricular contractions. The administration of atropine during the epinephrine paroxysm in the digitalized heart resulted in frequent interruptions of the tachycardia by short periods of normal sinus rhythm. Opportunity did not permit us to pursue further these observations on auricular paroxysmal tachycardia in the digitalized heart.

Auricular Paroxysmal Tachycardia, a Circus Movement Phenomenon.—The exact mechanism of auricular paroxysmal tachycardia has not been established. It is generally regarded as produced by a series of ectopic beats arising from an independent focus of impulse formation in the auricle. The observations recorded in this study are in harmony with the hypothesis that auricular paroxysmal tachycardia is a circus movement phenomenon. Its abrupt onset and cessation and the regularity of its rhythm support this view, and it differs from auricular flutter, established as a circus phenomenon, only in its slower rate and absence of A-V block. Given a ring of auricular muscle about which a circus can travel, an increase in the speed of conduction through the auricle or a decrease in the refractory period of the auricle, sufficient to permit reentry of a normal or an artificial impulse to contraction, will induce a circus movement. Lewis, Drury, and Bulger[5] have shown that the speed of conduction through the auricle depends essentially on the refractory period of the muscle. Therefore, in general, whatever will induce a shortening of the refractory period of the auricular muscle will favor the induction of a circus movement. Lewis and Drury[6] have demonstrated the dual effect of vagus stimulation on the auricle, the slowing action on the sinus region and the shortening of the refractory period of the muscle elsewhere in the auricle under certain conditions. A marked increase

in the heart rate tends to shorten the refractory period of the heart muscle.[5] It is probable that these factors are brought into play in varying degrees to shorten the refractory period of the auricle and favor the induction of a circus movement after epinephrine. The protection against an attack by quinidine also supports the theory of a circus movement since quinidine lengthens the refractory period of the auricular muscle, as Lewis et al[7] have demonstrated. On the basis of a circus movement phenomenon it is explainable that while a drug may prevent the induction of a paroxysm, it does not necessarily imply that it may stop a paroxysm after it has set in. A circus movement in progress is self-sustaining and, as we have seen, outlasts the action of epinephrine which produced it. While strong vagus stimulation may help to shorten the refractory period sufficiently to induce a circus movement, it does not necessarily follow that the removal of vagus tone will lengthen the refractory period sufficiently to abolish a circus movement in progress.

SUMMARY AND CONCLUSIONS

1. The effects of epinephrine, quinine, quinidine, atropine, and digitalis were studied in a patient subject to spontaneous attacks of auricular paroxysmal tachycardia.

2. Epinephrine induced attacks in this patient indistinguishable from those occurring spontaneously.

3. Quinine failed to abolish attacks occurring spontaneously or those produced by epinephrine.

4. Under quinidine administration spontaneous attacks did not occur, nor could they be induced by epinephrine.

5. Paralysis of the vagus by atropine accelerated the heart rate, but did not induce a paroxysm.

6. Paralysis of the vagus by atropine prevented the induction of a paroxysm by epinephrine.

7. The deduction is drawn that indirect vagus stimulation was an essential factor in this patient for the induction of a paroxysm by epinephrine.

8. Digitalis in a full dose did not produce an attack and did not prevent the induction of a paroxysm by epinephrine.

9. Attention is called to the fact that a drug may prevent the onset of an attack but be without effect in stopping a paroxysm in progress.

10. The observations in this study are in harmony with the hypothesis that auricular paroxysmal tachycardia is a circus movement phenomenon. The contradictory results obtained with drugs in auricular paroxysmal tachycardia by different observers depend, in part at

least, upon the fact that a number of factors may contribute to the production of the paroxysms and these factors vary in importance in different cases. There is also the possibility that not all cases of this tachycardia are produced by the same mechanism.

The authors acknowledge their obligation to Dr. John Wyckoff, on whose service this work was done, for his generous cooperation.

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[2]Galli, G.: Heart, 1920, vii, 112.
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THE TRANSFORMATION OF THE CENTRAL INTO THE PERIPHERAL PULSE IN PATIENTS WITH AORTIC STENOSIS*

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SOME of the most conspicuous modifications in pulse contour are found when the aortic orifice is either stenosed or the valves insufficient. The general character of these changes of the radial pulse has long been known. The pulse wave, which reaches the radial artery, does not have the contour which it possessed just beyond the aortic valves. Many factors have contributed to alter its shape (Frank[3]). It is important, therefore, to determine to what extent the deviations from normal, observed in the radial artery in patients with aortic stenosis, occur in transmission, and to what extent they are due to alterations in the form of the aortic pulsation.

If the pulse just beyond the aortic valves could be recorded and compared with a simultaneous radial pulse, the exact form imparted to the pulse by the left ventricle, and the extent to which this form is altered in transmission to the peripheral arteries, would be known. In man, unfortunately, the pulse in the aorta cannot be obtained. The closest point available is the second portion of the subclavian artery. A record obtained from this artery, while not devoid of alterations produced in transmission from the aorta, has these reduced to a minimum and gives a truer idea of the form of the aortic pulsation than does that from any other accessible artery (Wiggers[8]).

In this study of ten patients with aortic stenosis, therefore, the pulsations of the subclavian and of the radial artery were simultaneously recorded and their contours compared and analyzed. The method developed by Wiggers[8] was employed in taking these records, and the precautions which he gave were followed.

Typical records of simultaneous subclavian and radial pulses from cases with aortic stenosis are illustrated in Figs. 1 and 2. Both show all the radial pulse changes regarded as characteristic of this lesion; namely, the anacrotic wave or jog (Fig. 1), and the slow gradual ascent of each pulse beat, the so-called tardus quality. The descending limb, on the contrary, varies and its contour is apparently not determined by the valvular lesion. No vibrations of high frequency are present in these radial records. The pulse is smaller in volume than normally, but this cannot be measured quantitatively in sphyg-

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mographic records, where the amplitude is determined by spring and capsular membrane tensions.

A comparison of the radial pulse with curves recorded from the subclavian artery in simultaneous beats, shows at a glance certain obvious differences. These differences are clearly revealed in Figs. 1

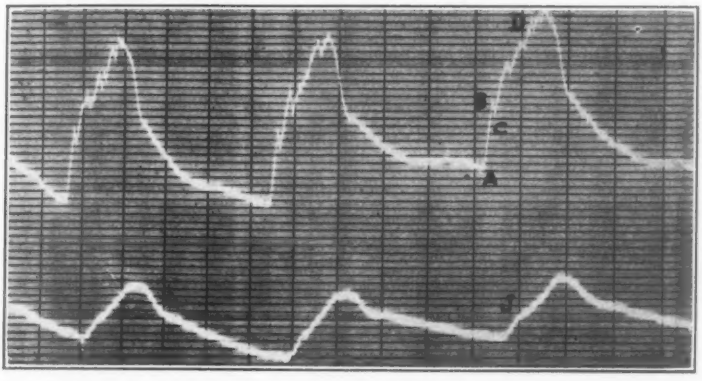

Fig. 1.—Simultaneous subclavian and radial pulses (actual size) obtained from a case with developed aortic stenosis (S. C.). Time in this and succeeding figures is ⅕ of a second. Description in text.

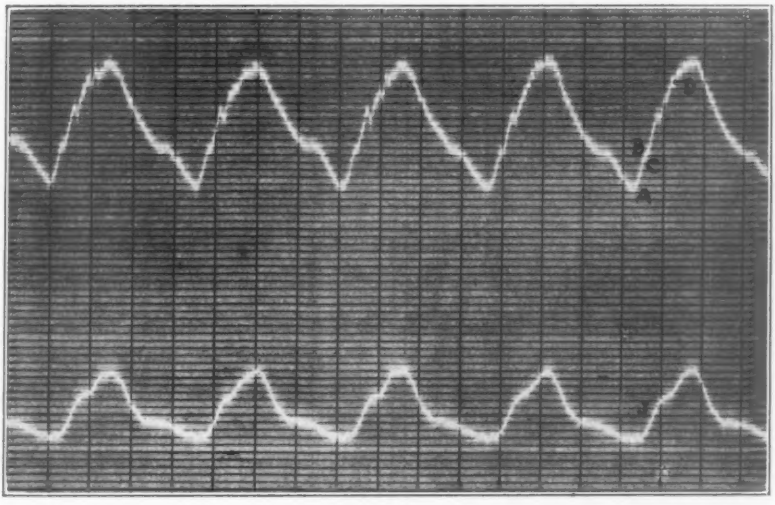

Fig. 2.—Simultaneous subclavian and radial pulses (actual size) obtained from a case with developed aortic stenosis (P.).

and 2, and perhaps more noticeably in the superimposed tracings of four cases, shown in Fig. 3 (curves A and D of this figure being traced from Figs. 1 and 2, respectively). A smooth anacrotic notch is present in the radial pulse and gives the impression that the pressure first rises for a time, then halts or dips for an appreciable interval and finally rises again to a summit; this is not seen in the

central pulse. This negatives all conceptions which assign a diphasic or double contraction effect to each ventricular systole, such as Nicolai[5] advanced, or those which postulate physical conditions supposedly operating to interrupt and split the actual ejection of blood, as Schonewald[6] suggested.

The subclavian pulse wave begins with a sharp, steep ascent (Fig. 1, A-B) which is in marked contrast with the slow rise in the radial pulse. This steep rise in the subclavian continues to a level

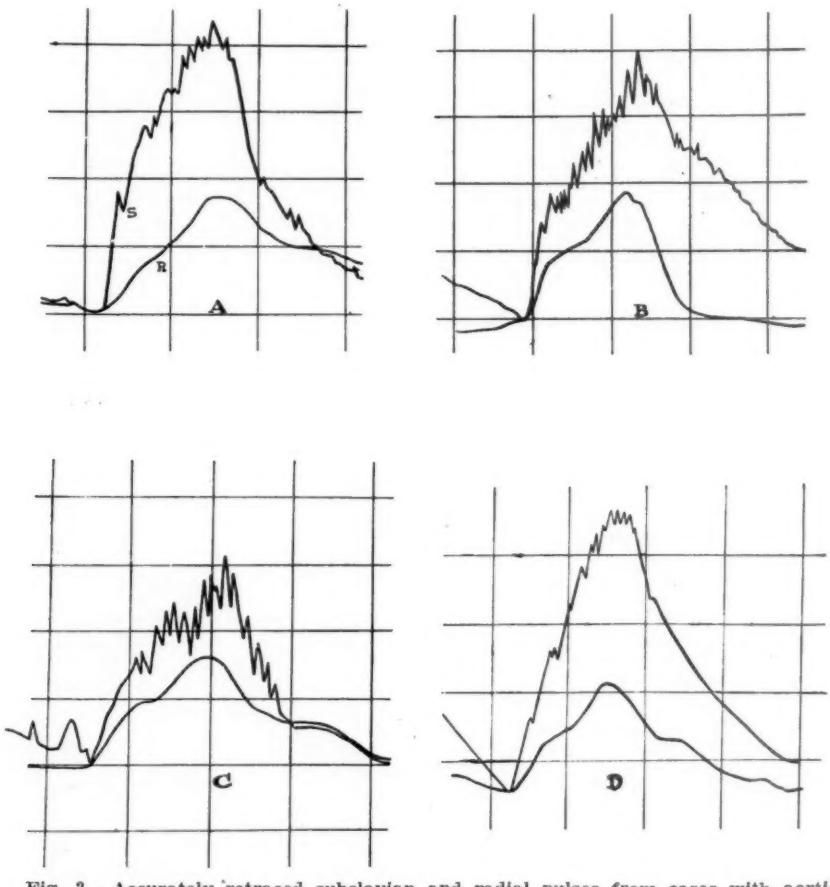

Fig. 3.—Accurately retraced subclavian and radial pulses from cases with aortic stenosis, superimposed so that the beginning of the upstrokes coincide, showing the time relation of other homologous points.

about ⅓ to ½ of the height of the upstroke. It ends in a sharp vibration similar in character to that occurring in the normal pulse, differing only in that this primary peak (B-C) occurs relatively low on the ascending limb instead of at the top. After this primary vibration the curve rises more slowly (C-D), differing from the normal in that the summit is not reached in midsystole but near the

end of systole. This slower rise has small vibrations, irregular in amplitude and period, which no doubt graphically represent the systolic murmur and thrill accompanying aortic stenosis.

As the initial part of the ascending limb is steep and significantly free from such vibrations, it appears that the velocity of ejection is not appreciably interfered with until the aortic pressure has been elevated to a certain level. Although the presence of the narrowed orifice tends to decrease the velocity of this early pressure rise, the effect is counterbalanced by the opposite effect induced by the increase in initial tension of the ventricle, which has been shown to occur in experimental stenosis, by De Heer[2] and Straub,[7] and is indicated in man by the prolongation of systole (of Katz and Feil[4]).

An analysis of the systolic murmur in a series of nine cases recorded with the sound capsules of Wiggers and Dean shows a delay in the appearance of the murmur, similar to that in the pulse. The data are given in the third and fourth columns of Table I. It will be seen that this delay averaged 0.091 of a second.

TABLE I

VIBRATION FREQUENCY OF SYSTOLIC MURMUR IN AORTIC STENOSIS AND TIME OF ITS APPEARANCE

CASE	RANGE PER SECOND	AVERAGE PER SECOND	DELAY PER SECOND	AVERAGE DELAY PER SECOND
G. Bat.*	149-260	174	.066-.122	.095
C. Gr.†	99-210	146	.074-.166	.114
S. C.†	135-146	140	.048-.163	.108
M. But.†	122-132	127		
J. Bu.†	111-147	125	.088-.161	.124
M. Ko.†	110-139	123	.059	.059
M. Bra.†	90-103	95	.043-.093	.072
J. LA.‡	25-40	31	.056-.092	.065
M. Ged.‡		20		
Average	90-260	133	.043-.166	.091

*Marked stenosis (Class III, cf., previous paper[5]).
†Moderate stenosis (Class II).
‡Mild stenosis (Class I).

The transition from a rapid to a slower rate of ejection occurs at a lower level in aortic stenosis than normally because the full force of the ventricle is not expended in ejecting blood, but is in part spent in overcoming the resistance of the narrowed orifice. The level at which the transition occurs is an index of the amount of stenosis and of the ability of the heart to overcome it.

Despite the fact that the central and radial pulses show many points of contrast, it is readily understandable, after Frank's[3] analysis of the conversion of the central into the peripheral pulse, how the characteristic changes in the peripheral pulse are produced. The smoothing out of the radial pulse, and the elimination of the fine vibrations result, because the arterial tree is essentially a periodic

manometer of low vibration frequency and, hence, does not transmit accurately the changes in pressure which are produced in the aorta. There can be little doubt also that the anacrotic wave of the radial pulse bears the same relation to the sharp interruption of the subclavian pulse that the dicrotic wave, on the descending limb of the radial, bears to the incisura of the central pulse. The anacrotic and dicrotic waves are both initiated by sudden changes in the gradient of the pulse curve in the central artery; both are intensified by resonance effects as the pulse wave is transmitted peripherally through the vascular system.

Further evidence that the sudden break in the subclavian pulse low down on the ascending limb is necessary for the appearance of the anacrotic wave in the radial pulse is shown by the pulse curves of aortic stenosis with auricular fibrillation. We were fortunate in

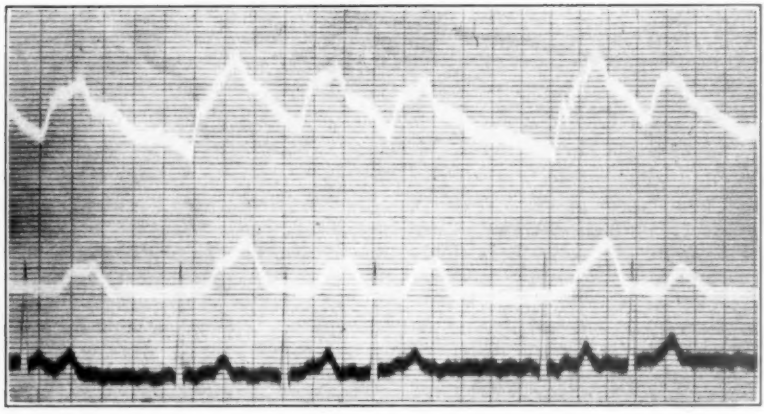

Fig. 4.—Simultaneous subclavian and radial pulses (reduced ⅔) as well as the electrocardiogram (Lead II), obtained from a case with developed aortic stenosis complicated by fibrillation of the auricles.

having two such cases in this series; the records of one are shown in Fig. 4. These curves show that following the longer diastoles a typical anacrotic radial pulse is seen, and when the corresponding subclavian pulse is examined, it is found to have the characteristic contour already described. On the other hand, when the beat follows a short diastole the radial pulse has no anacrotic wave, i.e., the last beat of Fig. 4 and, similarly, the contour of the central pulse approaches the normal.

The transmission time of the various parts of the pulse wave was examined and it was found that, as in the normal pulse, the summit travels faster than the foot of the ascent. This can be readily seen in Fig. 3, where the radial and subclavian pulse curves were set so that they start from the same foot points. The more rapid transmission time of the peak is shown in this figure by the attainment of

the summit earlier in the radial than in the subclavian. When like analysis is made of the anacrotic wave it is found to occur later in the radial pulse than in the subclavian (i.e., compare S. and R. in Fig. 3-A), indicating that this part of the wave front travels at a slower rate to the radial than the foot of the ascent. It is difficult to reconcile this fact with Bramwell's[1] conception of the transmission of the wave front.

SUMMARY

The subclavian and radial pulses in patients with aortic stenosis were recorded simultaneously by the recently developed optical method. The contours were studied and analyzed with special reference to the transformation of the subclavian into the radial pulse.

The graphic record of the subclavian pulse shows first a steep ascent ending in a sharp vibration about one-third of the way up the ascending limb; the rise following the vibration is less steep and has its peak near the end of systole. Small vibrations, irregular in amplitude and period, surmount the slower ascent but are significantly absent in the initial rise.

The transformation of the subclavian into the radial pulse characteristic of this lesion is described and the factors responsible for this change are analyzed.

Evidence is given to show that the anacrotic wave in the radial is the peripheral manifestation of the sudden break of the subclavian pulse occurring early in the ascent, the relation being the same as that existing between the incisura of the normal subclavian pulse and the dicrotic wave in the radial.

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CARDIAC PAIN

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VISCERAL and cardiac pain is the expression from the viscera to the central nervous system of afferent impulses which are usually inhibited, and do not come into consciousness. The central resistance may be sufficient to inhibit these impulses, which impinge on segments of the spinal cord, or at any rate to prevent the disturbance of consciousness; but, as Head emphasizes, if the impulses are sufficiently intense, and of long standing, pain is then projected to those parts of the surface of the body supplied by the spinal nerves corresponding to the segments, and these areas may then become tender, reacting to any disagreeable stimulus.

The more chronic a referred pain becomes, the more it spreads in and beyond the body segment. Not only is the general resistance of the patient worn down by disease, but the passage of painful impulses is facilitated by habit; hence impulses which previously failed to excite pain can now do so. A sudden rise of temperature frequently causes widespread generalization of pain; anemia is another cause of diminished general resistance to pain; exhaustion and anemia are not more potent than fear and anxiety in increasing the spread of pain. The extent of this automatic control over sensory impressions not only varies from time to time in the same individual, but is subject to extreme temperamenfal differences between individuals.

In all cases, therefore, the pain originating in some definite and recognizable cause spreads widely because of its severity and the long duration of the stimulus, or in consequence of the relaxation of central control, or from some debilitating psychological state, such as anxiety or emotional shock.

Neurotic pains, and pains of slight degree, originating from a visceral origin referred to the precordial region, may easily bring about a condition of fright and worry through their supposed connection with the heart, and thus induce a widespread distribution of pain through its long continuance and through the intense fear of sudden death, aroused in the patient merely through the position of the pain. The fear of sudden death from heart disease is an ever-present fear in many nervous patients; and Head's explanation of the causation of the spread of pain and the expected spread in the same segments that are supplied by the spinal nerves of the precordium would account for many attacks of so-called pseudo-angina. A cardiac pain, of however slight a degree, or of however great in-

tensity, must be expressed by the same nervous mechanism, the intensity of the stimulus causing different radiations in the various segments of the spinal cord, to which go the various afferent nerves from the different portions of the heart.

ANATOMICAL AND PHYSIOLOGICAL ASPECTS OF CARDIAC PAIN

To understand the nervous mechanism of the heart, with its afferent sensory tracks and their complicated passage upward through

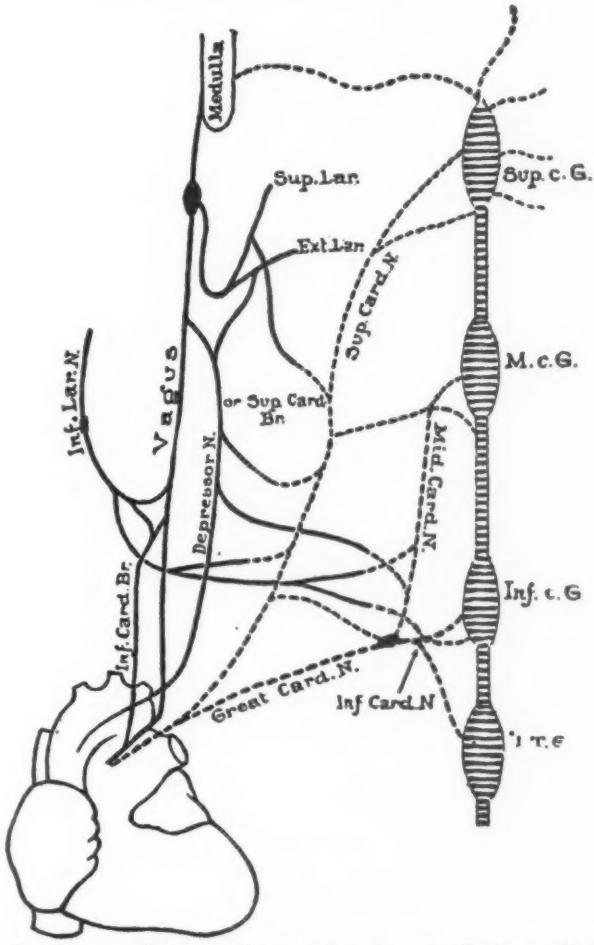

Fig. 1.—Anastomoses between the vagal and sympathetic cardiac nerves.

both vagus and sympathetic system, one must understand both the anatomy and physiology of the separate portions of this combined vegetative nervous system.

The nerve supply of the heart is derived from the three sympathetic nerves and the cardiac branches of the vagus. The superior cardiac nerve on the right side is often absent, and the entire cardiac

nerve supply frequently shows wide variations from its usual description. The superior, middle and inferior sympathetic nerves arise from their corresponding ganglions, or the sympathetic trunk. The superior and middle cardiac nerves, as they descend, anastomose with each other and with the superior and inferior cardiac branches of the vagus and with the superior and inferior laryngeal nerves. The inferior cardiac nerve arises from both the inferior cervical and the first thoracic ganglions or from their combined stellate ganglion. It anastomoses with the recurrent laryngeal nerve and frequently joins with the middle nerve and a branch from the superior nerve

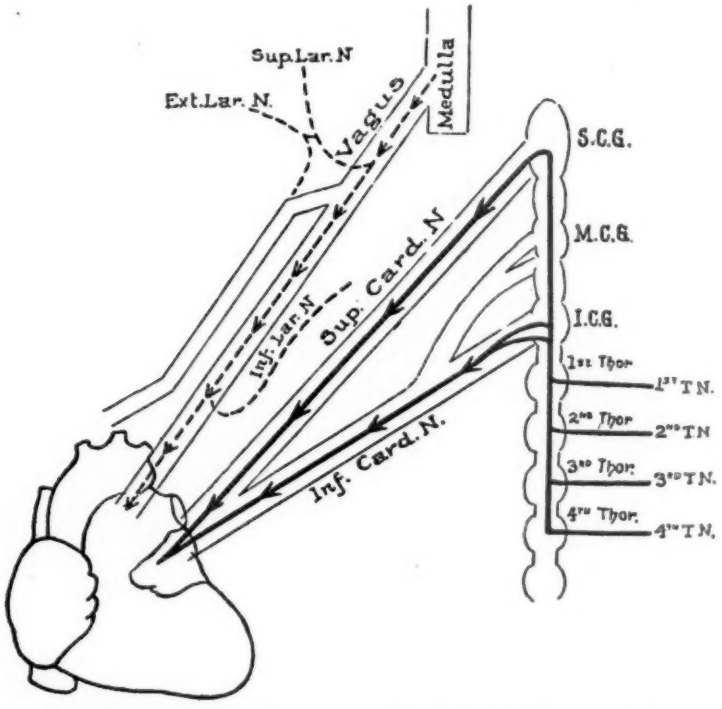

Fig. 2.—Cardiac motor nerves, vagal inhibitory and sympathetic accelerator.

in a five-cornered ganglion, and then all go as one great cardiac nerve to the deep cardiac plexus.

Whether or not there is a depressor nerve in man, as first described by Ludwig and Cyon for the rabbit, is a mooted question. In animals, arising by the root from the superior laryngeal and by another root from the trunk of the vagus, the depressor nerve continues downward as a separate nerve. The opinion of most investigators agrees with the description of Tandler that the depressor nerve in man is represented by the superior cardiac branch of the vagus which almost constantly receives a root from the external laryngeal branch of the superior laryngeal nerve. It runs to the superficial cardiac

plexus, either alone, or joined with the superior sympathetic nerve. The depressor is considered an aortic nerve, the endings of the left side going to the anterior and those of the right to the posterior surface. Tschermak states that the depressor is distributed especially around the first portion of the ascending aorta. According to Köster and Tschermak, the cells of the depressor fibers are found in the jugular ganglion of the vagus.

In general, the vagal portion of the vegetative nervous system carries cardiac inhibitory fibers, and the sympathetic portion the accelerator fibers. The two portions are antagonistic in their efferent fibers, but both portions carry afferent fibers.

The main sympathetic cord is formed of afferent and efferent fibers. The efferent fibers go to the sympathetic ganglions to join their neurons and are relayed as gray nonmyelinated rami to the spinal nerves, carrying vasomotor and secretory fibers. To each spinal nerve go one or more gray rami from the sympathetic ganglions. The afferent or visceral sensory fibers arising in the spinal cord go up and down the sympathetic cord, and pass through the ganglions, without further neuron connection, out to the viscera. These myelinated efferent and afferent fibers form the white rami. The cervical nerves possess no white rami, as these nerves are only connected with the thoracic and first four lumbar nerves. The cervical portion of the sympathetic trunk consists almost exclusively of ascending fibers, but there are also important branches resembling gray rami going to certain cranial nerves, and to the heart, pharynx and thyroid and carotid arteries, carrying vasomotor and secretory fibers to the thyroid and salivary glands, to the eye and to other structures. These gray, postganglionic fibers are especially abundant from the superior cervical ganglion. The afferent sensory nerves carry pain into the posterior spinal nerve root and through its posterior ganglion into the spinal cord, and up to the thalamus. The sensation of pain can arise in consciousness from the thalamus without going to the cortex. The fibers of the vagal system go uninterruptedly from the cerebrospinal origin to the ganglions in or near the viscera, and are relayed onward from these plexuses.

To comprehend the mechanism of relief from the intense pain of angina pectoris, through surgical interference by section or removal of the various parts of the cardiac vegetative nervous system, necessitates a very accurate conception of the physiological function of the various afferent and efferent pathways.

The important efferent function of the sympathetic nervous system is that of the accelerator fibers. These arise from the second, third and fourth dorsal nerves and, passing upward to the first thoracic and inferior cervical ganglions, go to the deep cardiac plexus and heart by the inferior cardiac nerve. Ransom states that some accelerator

fibers pass to the heart by the way of the superior cardiac nerve. The most complete discussion of the afferent cardiac fibers and the physiology of the innervation of the heart is given by Danielopolu of Bucharest in his treatise on "Angina Pectoris." This author describes the sensory cardioaortic fibers from the heart and aorta and divides them into two main groups. The first group crosses through the stel-

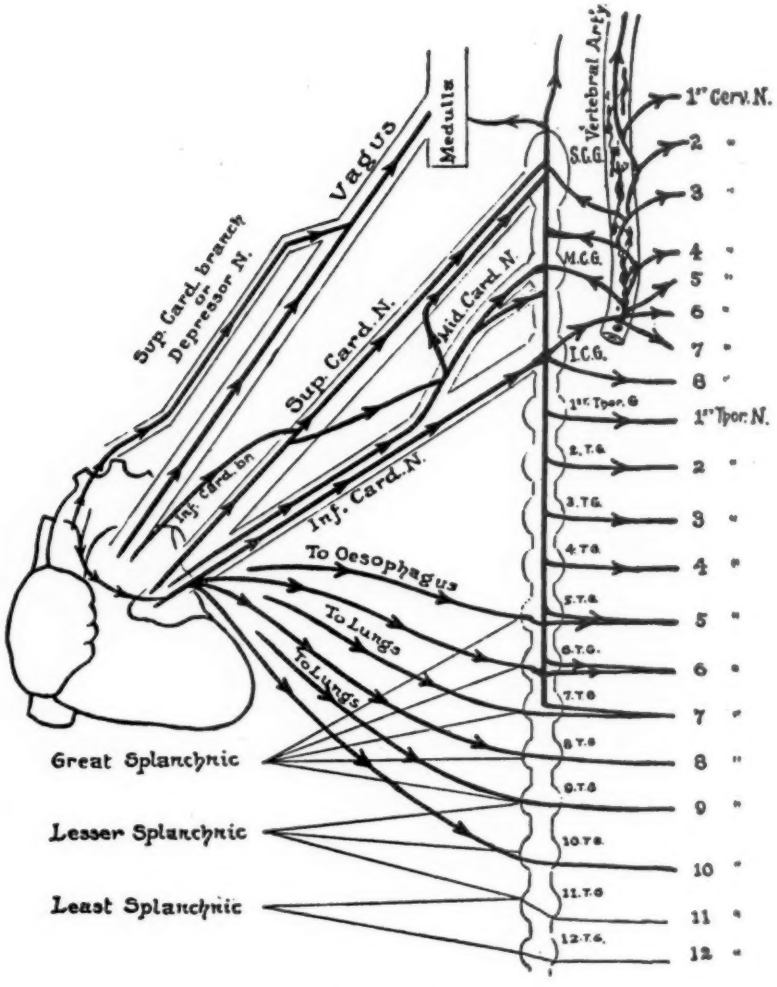

Fig. 3.—Cardioaortic sensory afferent nerves.

late ganglion and divides into several bundles. Two of these bundles go to the spinal nerves from the sixth cervical to the fourth dorsal. Another bundle, forming the plexus on the vertebral artery, sends fibers up the main sympathetic trunk and branches to all the cervical nerves, as it follows the artery upward. Another bundle goes in the cervical sympathetic trunk, uniting with fibers coming in from the

superior and middle cardiac nerves and from the vagus. The fibers of this last bundle pass into the first five pairs of cervical nerves, the cranial nerves and the medulla, and by the carotid and cavernous plexuses into the gasserion ganglion.

The second main group of the sensory cardioaortic fibers, without crossing through the stellate ganglion, follows the cardiac nerves of the sympathetic and the cardiac branches of the vagus, separating in two bundles. One bundle, following the superior and middle cardiac nerves to the cervical sympathetic trunk, unites in this trunk with the bundles belonging to the first group. The other bundle runs in the vagus and its cardiac branches, some of its fibers by the depressor nerve, other fibers through the recurrent laryngeal, others through the inferior cardiac branches to the main trunk of the vagus. Some of these fibers even cross over, by anastomoses, to the sympathetic trunk. In discussing the effects of surgical operations already performed, we shall return to this description. If we add to the above sensory paths the afferent visceral fibers to the middle dorsal nerves, which arise from the same segments as the splanchnics but go to the aorta, lungs and esophagus, we can understand the pain encountered clinically in the epigastrium as cardiac pain. Tandler and Manouélian describe an abundant distribution of sensory nerve endings in all layers of the heart and in the wall of the aorta.

There are certain vasomotor reflexes controlled by the vegetative nervous system which are important in angina. Afferent fibers which cause depressor reflexes excite the vasodilator center and simultaneously inhibit the vasoconstrictor center. Bayliss also states that without doubt the depressor endings are stimulated by a rise of aortic pressure, a general fall of blood pressure resulting, since a depressor stimulation affects all vasomotor nerves and there is no antagonism in general reflexes between visceral and peripheral circulation. But with the exception of the depressor nerve, all afferent nerves contain fibers whose stimulation results in a reflex rise of arterial blood pressure. Such a rise of pressure appears from stimulation of nerve fibers carrying the sensation of pain from the excitation of vasoconstrictor nerves and the action of the vasoconstrictor center. Sherrington points out that the muscular coats of the arterioles may be justly regarded as the physiological antagonist of the cardiac muscle: any increase in the strength of the cardiac contraction would be accompanied by the inhibition of the tone of the vascular musculature.

Cardiac pain of all intensities, from the transitory uneasiness in the precordium to the most intense agony of Heberden's angina, can only be explained by irritation or pathological stimulation of the sensory nerves or nerve endings of the heart and aorta. How richly endowed the heart and aorta are with these same sensory nerve endings has just been said. Neither muscle fibers nor connective tissue

nor blood vessels can transmit the sensation of pain except through their sensory nerve supply. Neither spasm nor cramp nor stretching of these tissues, nor yet fatigue, exhaustion, nor the chemical products resulting therefrom, unless these products act upon the sensory nerve endings, can explain pain which is produced only in sensory nerves. Neither spasm nor claudication of blood vessels produces pain except as they cause pressure on sensory nerves and their endings, or sudden deprivation of their blood supply. The pressure on sensory nerves or their endings, from any cause, or the sudden deprivation of blood supply causes all gradations of pain anywhere in the body and one does not have to go outside of these processes to explain cardiac pain and Heberden's angina.

CLINICAL OCCURRENCE OF CARDIAC PAIN

Clinically, cardiac pain occurs with those pathological lesions which produce an increase of scar tissue or sudden diminution or cessation of blood supply in the tissues of the myocardium and aorta. Acute myocardial inflammations, acute endocardial infections do not give pain. Chronic degenerative inflammation of the cardiac muscle fibers and chronic valvular lesions do not give pain unless the aortic tissues are also involved above the aortic valves or the chronic inflammation around the mitral opening has produced a cicatricial contraction of chronic stenosis. Pain does not accompany the cardiac irregularities either with the toxic extrasystoles or the degenerative processes producing auricular flutter or fibrillation, or heart-block or bundle-block. The auricle and ventricle may be completely dissociated and pursue for years their painless arrhythmic beating. Neither cardiac hypertrophy nor dilatation gives pain; the occurrence of dilatation may even cause a cessation of attacks of pain. But when septic, rheumatic or syphilitic degenerations have destroyed myocardial muscle fibers and connective tissue scars replace the muscle fibers, sensory nerves can be caught in the healing cicatrix and the pressure requisite to produce pain is conceivable.

When the chronic coronary sclerosis of arteriosclerosis or of luetic infection produces coronary endarteritis and the vessels lose their resiliency and their lumen slowly and surely narrows till the final occlusion comes and the sensory nerve endings are suddenly deprived of their blood, terrific pain may occur, even when the resting body has called for no increase of cardiac exertion. Coronary sclerosis from whatever cause is not confined to the larger vessels. It is a pathological process extending out into the finest capillaries and often chiefly active in these minute vessels. When a capillary or tiny artery is occluded, the small area dependent on its blood supply dies, and is absorbed and replaced by connective tissue; this must apply to both muscle cells and sensory and motor nerve endings. Since this process is continuously occurring in sclerosing hearts, with no afferent painful impulses ap-

pearing in consciousness, the obliteration of such tiny areas is usually insufficient to cause pain. Less than 25 per cent of 325 patients who died of final coronary occlusion and rupture of the heart wall had had any previous warnings of sufficient intensity to suggest disease of the heart. If, however, the blood supply is suddenly cut off from a sufficiently large cardiac area involving many sensory nerve endings, pain is produced, whether the deprivation of blood supply has been produced by the extra demands of bodily exertion or by vascular occlusion at night, when the body is at rest.

Postmortem examinations have shown that the same sclerotic processes occur simultaneously in the heart and aorta, or the lesions may be confined to either, or may predominate in one or the other. The same afferent nerve supply is disseminated on the aorta and in the heart, and the same afferent pathways carry sensations of cardiac pain or the agony of angina pectoris.

CLINICAL PATHS OF CARDIAC PAIN

The functional processes producing pain are unknown. We are only beginning to know accurately the pathways through which the disagreeable sensation is carried up to the thalamus and on to the cortex, to be recorded in consciousness.

Cardiac pain is registered in those segments of the body and spinal cord which embryologically were originally connected with the primary cardiac tube. Aortic pain is registered from the upper part of the cardiac tube in the first four cervical segments from the upper thorax and up in the throat and neck and pharynx or even the jaw, or shoots like a stabbing thrust over the scalp through the lesser and greater occipital nerves. With greatest rarity does pain seem to spread down below the shoulder area of the fourth cervical nerve. Cardiac pain rarely, indeed, is felt in the segments supplied by the fifth, sixth and seventh cervical nerves which supply the outside of the arm; the cardiac afferent nerves do not connect with these spinal nerves, or else they go through the ganglion of the posterior root in the afferent tracts without receiving ganglionic connections which would cause pain reflexes in these segments. Pain from the middle portion of the original cardiac tube, forming the adult ventricles of the heart, is registered in the segments of the eighth cervical and the first five dorsal nerves, substernally or high on the precordium at the level of the third and fourth ribs or radiating to the shoulder or to the back, or in the back by the posterior branches or down the inner side of the arm to the elbow, wrist or finger tips in the ulnar nerve. Pain from the auricle is registered in the sixth and seventh dorsal nerves on the lower part of the chest and precordium, as the auricle was originally the lowest portion of the original cardiac tube; this lowest portion, by bending upward and revolving, came to lie between the aortic upper and ventricular middle portions.

Some forms of cardiac pain and some attacks of so-called abdominal angina are registered below the angle of the ribs in the epigastrium. This is particularly common in sclerosis of the coronary arteries. This epigastric pain seems to be a reflex through the aortic and deep cardiac plexuses, to the middle thoracic segments, depending perhaps, upon the area of the aorta or heart from which the afferent impulse starts. Any afferent impulse, if sufficiently intense, produces the sensory motor reflex emphasized by MacKenzie. The motor nerves of the implicated segment then produce a muscular rigidity, giving a sense of thoracic constriction or tightness or vise-like compression.

With cardiac pain there is often a sense of impending death or at times an intense fear of death, or, in very severe anguish, the conviction or even hope that death will soon bring relief. Sometimes, even with slight intensity of the pain, there is an uncanny certainty of the seriousness of its meaning, more than fear of its recurrence or dread of its intensity. This seems a reaction in consciousness, of thalamic connection with the cortex rather than of spinal reflex. The strongest of all primary instincts is that of self-preservation, and the associated ideas of the serious prognosis in cardiac disease and the frequency of sudden cardiac death are all intimately associated in consciousness, linking the sensation of cardiac pain with impending death.

Soon after Heberden, in 1768, first described the anginal syndrome, Jenner and Parry described postmortem examinations of patients dying of angina and found sclerosed and calcified coronary arteries. They inferred the causal relationship of the coronary disease and the anginal pain. Shortly afterward, however, two further postmortem examinations in patients dying from angina showed normal coronary arteries and myocardium with, in one instance, only moderate disease at the proximal aorta and in the other extensive atheromatous lesions of aortic valves and the adjacent aorta. Not for over a hundred years, until Sir Clifford Allbutt emphasized the frequency of aortic, with absence of coronary, lesions, was the frequency of the aortic origin of Heberden's angina realized. The great frequency of all degrees of cardiac pain, the frequency of sudden death associated with coronary endarteritis, often prevented a differentiation between angina pectoris and the certain small percentage of coronary sclerosis which showed the anginal syndrome. Only in recent years has the clear-cut clinical picture of coronary sclerosis with its terminal coronary thrombosis been delineated. It has clinically become increasingly evident that the usual myocardial disease is not accompanied with pain, that in chronic valvular disease the anginal syndrome is of great rarity except in cases with lesions of and around the aortic valves, that in many patients suffering from angina, as the heart has failed and dilated, the pain has ceased; as Wenckebach expresses it, "what damages the heart muscle wards off angina."

The recent work of Christian, Nathanson, and Nuzum and Hagen has done much to extend the observations of Herrick and Libman and to connect the clinical symptoms with the lesions of coronary sclerosis. The work of Hamburger, Priest and Bettman has extended the scientific knowledge obtained by Porter and Gold from the experimental occlusion of the coronary circulation.

CORONARY ENDARTERITIS

Coronary endarteritis may be of syphilitic or arteriosclerotic origin, the luetic cases usually occurring at an earlier age than the arteriosclerotic. Rare, indeed, before forty years of age, it occurs with increasing frequency until just before the seventieth year of life, when the frequency of its occurrence diminishes. It occurs more frequently in men than in women. The resulting lesion is a myocardial degeneration with connective tissue replacement, but, because of the progressive obliteration of the blood supply, it manifests itself differently from the usual chronic myocardial disease.

In about 80 per cent of the cases the symptoms are those of attacks of pain and dyspnea, and not the gradual onset and increasing cardiac disability of the usual myocardial failure. The latter course is present, however, in about 20 per cent of the patients. The pain is not the stabbing apical pain so common in neurotic patients, nor the precordial soreness and sharp pain of tobacco intoxication, but is characteristically a sense of fullness and pressure or an uncomfortable oppression or constricting belt, rather than an acute, sharp pain. The pain is usually substernal or precordial, but only in 10 per cent of Nathanson's cases did it radiate to the shoulder and arm. In a few instances, however, the pain remains localized in the shoulder and arm. More than twice as frequent as arm pain is epigastric pain. In these attacks, whether the pain is substernal or epigastric, there are frequently nausea and vomiting and belching; hence the frequency of so-called fatal "acute indigestion." The attacks of dyspnea bring with them a sense of suffocation and choking and not the increasing intensity of dyspnea on exertion. The attacks of respiratory distress occur even in patients who show but little dyspnea on exertion, and often occur during the night. Nathanson reports one patient in whom the substernal distress was relieved by exertion.

Examination of the patients may show normal blood pressure and normal-sized heart with no murmurs and good heart sounds; but in the majority of patients there are hypertension and an enlarged heart, with diminished or distant heart sounds. The urinary and blood examination is usually normal. The disease runs its course, in most instances, hampering the individual afflicted either with attacks of pain or respiratory distress, or with these symptoms combined, but otherwise not interfering with his activities until the

endarteritis has obliterated the lumen of some large vessel; in which case the patient may die suddenly in one of his attacks, or there may occur a thrombosis of the artery with its fairly constant picture. Many patients, however, show finally a breaking-down of the right ventricle with congestion of the liver and general edema. Some patients die of left ventricular failure and edema of the lungs. The attacks of pain and dyspnea are apt, however, to differentiate such cases from those dying of the usual cardiac decompensation.

Coronary thrombosis occurs in about one-fifth of those suffering from coronary endarteritis, coming on suddenly and often without previous warning of any serious cardiac disease. It is a very common cause of sudden, unexpected death, apparently from ventricular fibrillation; or the patient may live a few minutes or hours. Not infrequently the patient lives a few days or weeks, dying suddenly when the heart ruptures through the softened infarct. About one-third of the patients who suffer from attacks of coronary thrombosis recover; in such cases the occluded vessel has fortunately not been too large or has possessed abundant anastomoses.

In a small number of patients the thrombosis occurs without pain. The patient is found in collapse, with a sense of impending death, his ashen gray face suffused with cold sweat, and often suffering from great respiratory distress or intense dyspnea on the slightest movement. Most of these patients suffer intense tearing pain or a deep-seated substernal agony. Frequently the pain radiates to the left arm and left side of the neck, or to both arms; but with characteristic frequency the pain is subdiaphragmatic and in the epigastrium, and the patient then gives the picture of acute abdominal visceral perforation. Of if the pain is on the right side and radiates through to the back, the picture is that of biliary colic with collapse. With the intense suffering the sweating face is pale, pinched and drawn with apprehension, sometimes cyanotic. The pulse is of poor quality, usually very frequent, often arrhythmic. The blood pressure is always low; frequently the systolic pressure is below 100. Systolic murmurs are often present but are of no significance. Christian draws attention to the frequency of crackling râles widely spread over the bases of both lungs, indicating the left ventricular failure and acute pulmonary edema. There may be slight fever of 101° to 102° F. A leucocytosis of 10,000 to 15,000, even to 25,000, with 81 per cent to 83 per cent polymorphonuclear leucocytes, is practically always present and may occur within two hours of the infarction. The abdomen may show distention with slight muscle spasm in the epigastrium or right hypochondrium. The liver is often tender and slightly enlarged. The electrocardiogram, when it is possible or wise to obtain one, may be normal, or may show any deviation therefrom produced by previous disease. In experimental coronary occlusion, and clini-

cally in some of these patients, an electrocardiogram occurs, which is not seen in other conditions. This consists in a downward deviation of the T-wave in one or more leads, with the ST or RT interval tending to show a rising point in opposite direction to the inverted T.

Some patients, however, with coronary occlusion, have shown only a diminution in the amplitude of the QRS group, and the inverted T-wave.

The electrocardiogram immediately following the occlusion of the artery may differ widely from those obtained during convalescence, and after the scarring of the tissue and healing has occurred.

A characteristic localized pericardial rub may develop in those patients who live forty-eight hours or more.

The patients with this underlying pathological condition should be differentiated from those with the syndrome of Heberden's angina pectoris, who are usually suffering from aortitis and who often fail to show the cardiac and coronary lesions produced by coronary endarteritis.

HEBERDEN'S ANGINA

One of the most characteristic peculiarities of Heberden's angina is that the pain is of such character that the patient is forced instantly to stand still or remain where he is. With this there is no dyspnea, but a cessation of breathing, as if the patient were afraid to breathe, and the pulse is slow and regular. The pain begins as a dull, grinding, tearing pain. After an attack, when asked where it was, the patient does not put his hand indefinitely over the precordial area or point with a finger at the apex saying it was a sharp, stabbing pain, but points to the left side of the chest above the sternum or over the xiphoid. The patient never treats it lightly, but, with serious demeanor, speaks of it with fear and respect. Beginning deep in the chest as substernal, the pain radiates up to the arm and shoulder and down usually the left arm on the inside to the elbow or on to the wrist, and ring and little fingers. At times it begins in front and goes through with a burning sensation into the back and then up on the shoulder and down the arm; or it seems to occupy the whole chest and radiates into and down both arms. At times the pain goes more up into the neck and throat, beginning as a clutch under the jaws, and extends up into the area behind the ears and even radiates into the jaws or shoots with a terrific thrust to the top of the head, running along the great occipital nerve on the back of the scalp. At times the pain is only localized in the wrist or it may appear as a burning ache inside the arm and not felt in the chest. Or it may remain as a burning, intense pain in the chest and not radiate in the arm. It may be felt only at the insertion of the accessory nerve into the trapezius and in the third or fourth left intercostal space and in

the great occipital nerve. In a few patients it radiates down into the epigastric region or, beginning in the back, radiates forward and around the intercostal nerves. In rare instances it seems to be limited to the right side. Danielopolu and Danielescu report that in a case of total inversion of the viscera, with angina, the pain radiated to the right side.

Dyspnea does not belong to angina. There is often a feeling of constriction which makes respiration nearly impossible. Or the patient may very carefully draw his breath slowly, fearing to move in the slightest degree lest the agony increase. In many cases the pulse remains normal and the heart does not quicken its rhythm. Often in the most intense attacks the heart beats quietly until, just before death, it suddenly becomes arrhythmic. In other attacks the pulse becomes full, though regular, and may beat as infrequently as 28 or 30 to the minute. In these cases the heart feels to the patient as if it were bursting or had suddenly stopped. It is rare in typical angina to have the pulse irregular until just before death.

There may be nausea and vomiting with the beginning of the attack. There may be sudden over-filling of the mouth with saliva which may run down the corners of the mouth. The face is pale and looks pinched and drawn and the perspiration runs down the face from the forehead.

With the intense pain there is the angor animi or fear of approaching death. In many patients it is expressed as a certainty of approaching dissolution rather than the fear of it, because they do not care to live and suffer so much. The feeling may be one of intense apprehension and anxiety. This fear of death with its horror is less pronounced in young persons and is often absent. The relation between the intensity of the fear of death and the intensity of the pain does not run parallel. Often the sense of impending death comes with but slight pain, or it may be entirely absent, even with the most intense pain. Not infrequently in the first attack, with but a slight constriction of the chest, there comes a peculiar creepy horror into consciousness that the number of one's days is fulfilled. Frequently, when death seems most inevitable, the patient describes it as waiting in benumbed agony, hoping that the end will come and blot out the suffering. The pain may last but a few seconds and the attack subside, or it may last for some minutes or even for a longer time. Usually, as the attack passes off, the pain in the chest subsides first, then the arm pain ceases, but the numbness in the arm disappears more slowly.

These attacks are usually brought on by exertion, especially in the beginning, and the patient soon learns at the slightest beginning of the pain to stop until it passes over. This is very apt to be the case in walking after a meal, or in walking against the wind and more frequently from walking up an inclined plane than upstairs. Often

with these slight attacks there will be an eructation of gas and the pain instantly ceases. Later any exertion, that of dressing or writing, even chewing, causes a paroxysm, making life nearly unbearable.

Wenckebach says that in the great majority of cases three conditions bring on paroxysms: a full stomach, worry and cold. Emotional excitement, such as nervousness, alone or combined with physical exertion, worry over catching a train, fear because the nitroglycerine has been left at home, any nervous irritability brings on the pain. Cold weather or going into a cold room increases the suffering; leaving a warm room and going out into the cold invariably starts pain; undressing in a cold room and getting between cold sheets will bring on an attack; anything which stimulates the action of the heart, demanding an increase of output, or anything raising blood pressure causes pain. Remove the disturbing factor and the attack will subside as quickly as it came.

Physical examination does not necessarily show anything characteristic. Often there may be an enlarged aorta or an enlarged heart, or these may be absent. There may be arteriosclerosis with high or low blood pressure. The prognosis in these patients is better than in those patients suffering from coronary thrombosis with the same syndrome of pain. These types of angina are designated as the chronic forms, although the attacks may be acute enough. Only a small percentage die in the first attack. Patients who have had one attack, however, if they wish to live for a number of years, will have to avoid mental excitement and full meals; they will have to be temperate in all things, abstinent in some. They cannot even enjoy the luxury of losing their tempers, and the luxury of tobacco must be foregone. There seems to be no question that tobacco increases the frequency and the intensity of true anginal attacks.

Most patients die suddenly; but a great deal can be done for many patients to relieve them and improve their condition, especially those who are suffering from syphilitic disease of the aorta. This type yields readily to proper treatment.

It is evident that the difference between the anginal syndrome in Heberden's angina and that produced by coronary disease is that while the position and radiation of the pain may be the same, for the same afferent nervous system conducts the painful impulses in both conditions, it is more frequent in the epigastrium than in the arms in coronary disease. In coronary disease dyspnea is rarely absent during the attack, often accompanied by collapse, with a frequent, thready pulse, often arrhythmic. In true angina the pulse is regular and full, with no dyspnea. In angina the lungs usually remain clear. In coronary attacks they very frequently show fine râles from acute pulmonary edema. Even with the intense pain of coronary disease the patient often does not show any characteristic attitude. He

may be nervous, moving about with intense apprehension. In angina the patient stands or sits still with his hand clutched to the most painful spot.

In coronary disease the pain is often of longer duration than in angina, and nothing except heavy doses of morphine will cause its cessation. Frequently in angina the nitrites relieve the paroxysm as quickly as it has come. The action of the nitrites is a characteristic test of real angina. The attacks of pain from coronary disease, with or without the acute respiratory distress, are apt to come at night or when the patient is quiet, and show no especial relation to exertion. Angina, in the early attacks, almost invariably follows exertion, and ceases with the exertion. Only later are attacks of real angina likely to come in the sleep.

OPERATIONS FOR RELIEF OF PAIN IN ANGINA

Of late years public health work has prolonged the expectation of life, and deaths from many infectious diseases have enormously diminished. But deaths from heart diseases have become more numerous. Heart disease is not necessarily on the increase, but more people live to acquire the diseases of senescence, and cardiac pain is more frequently met than formerly.

In recent years surgical interference has been suggested for the relief of pain of an anginal character. In considering these operations it is necessary to realize that if the pain, though typical of the anginal syndrome, be due to a coronary disease or thrombosis, the operation will probably not be well borne and perhaps of little value. In cases of real angina, on the other hand, with but apparently relatively little coronary involvement, operation has actually caused a great relief of pain and added years of usefulness to the lives of patients formerly incapacitated.

Danielopolu has gathered together the different operations already performed. The first operation was done by Thomas Jonnesco and was that of the removal of the three left cervical sympathetic ganglions and the first thoracic. This was done in five patients. The attacks of angina ceased, and had not returned in the first patient in seven years; in the second, eleven months, and in the third, eighteen months. But the last patient had an attack of acute edema of the lung some months after the operation. Two other patients succumbed four days after the operation, also with acute edema of the lungs.

Brünning, in Berlin, removed the same left cervicothoracic sympathetic chain in a case of angina. Three months after the operation there had been no recurrence of anginal paroxysms. Brünning relates that the systolic blood pressure, which was very high before the operation, fell afterward and in a few days was below normal and remained around normal elevation for several weeks.

The criticism of this operation is that it cuts off the main supply of accelerator fibers coming from the second and third thoracic segments passing through the inferior sympathetic ganglion to the heart. It also cuts off the constrictor fibers to the lung and, it is said, the vasomotor or vasodilator fibers to the coronary vessels. It does, however, extirpate the sensory fibers from the heart and aorta, which go along the vertebral artery into the cervical nerves, and the different fibers going up through the main cervical trunk to the superior ganglion and on to the cranial nerves; also the afferent fibers going down to the upper dorsal nerves. It also cuts off all possible passages of pain by afferent fibers through their vagal anastomoses with the three sympathetic cardiac nerves.

Danielopolu emphasizes, apparently with justification, that the heart is left under control of its inhibitory fibers and cut off from its accelerating fibers which not only regulate the rapidity of its action but which increase the conductibility and the contractility of the myocardium. After the extirpation of the inferior cervical and first thoracic ganglions, the heart slows and contracts superficially and without due force. The criticism of Brünning's operation and of his observation of reduction of hypertension thereby is that the fall of pressure occurred because of the same diminution of the contractile power of the left ventricle from the removal of the motor fibers of the heart. The attacks of acute edema of the lung fatal to two patients were, in the opinion of Danielopolu, brought about by the obliteration of these same motor fibers and the failure of the left ventricle therefrom.

Coffey and Brown, in this country, cut the superior cardiac nerve and also the sympathetic trunk above the inferior ganglion and suppressed the attacks. Eppinger and Hoffer cut the branch of the vagus nerve proceeding from the superior laryngeal nerve, which they believed to be the depressor nerve, and suppressed the anginal paroxysms. Shoehelin and Hotz cut the first cardiac branch of the vagus and suppressed the attacks. In these three different operations, that of Coffey and Brown cut the afferent fibers going up through the superior nerve into the superior sympathetic ganglion. The other two operations here were evidently successful endeavors to cut the depressor or pressor fibers running through the depressor nerve coming from the aorta and not from the heart, and probably also cut a certain portion of the sensory afferent fibers going up from the heart through the superior branch of the vagus.

Danielopolu and Hristide recommend the section of the cervical sympathetic trunk above the inferior ganglion as carried out successfully by C. G. and A. F. Jennings and Coffey and Brown, the latter two adding afterwards the section of the superior cardiac nerve.

Gino Piero cut the main cervical trunk above the inferior ganglion and also the fibers going onto the vertebral artery. The immediate

results were successful. This operation cuts the main afferent sensory fibers going up to the cervical nerves and also cuts all pressor fibers in the sympathetic cord.

Lilienthal resected the sympathetic cord including the superior ganglion but left the inferior and first thoracic. In these the results are reported as successful. Wenckebach reports the section of the depressor nerve for the relief of angina as having been performed in some 14 cases and that the operations were well borne. Two patients, however, died. In the first case double-sided angina ceased after the resection of the left depressor nerve, but in another operation performed on the right side, no isolated depressor nerve was found. The vagus was then divided below the exit of its inferior laryngeal branch. The pain disappeared, but a fortnight later the patient died suddenly without known cause. In the second case of right-sided angina, a depressor nerve was found and sympathectomy done. Five hours after the operation the patient died of pulmonary edema.

Recently Levine and Newton have emphasized the necessity of a selection of cases for this operation. They believe that all liability to coronary infarction in advanced coronary disease should count against the possibility of a surgical operation. In studying attacks of pain, they relied on the regularity and slowness of the pulse as against the frequent rapidity and changes in rhythm in coronary disease and on the fact that after an attack of angina, leucocytosis does not occur, but is characteristic of the presence of a coronary thrombosis, especially if low blood pressure be added. If there be myocardial changes sufficient to produce a congestive heart failure, the patient is not a good surgical risk. In all patients with syphilitic aortic insufficiency the electrocardiogram should show essentially normal complexes. There should be no gallop rhythm in the heart nor pulsus alternans. There should be but moderate increase in the size of the heart and only systolic murmurs. Applying these criteria to seven patients, Levine and Newton had them successfully operated upon—all were alive at the end of from two years to three months after the operation and all but one were improved. Four had no anginal symptoms at all; two had typical attacks of a milder nature than those previous to the operation, and one was neither better nor worse. One patient with a syphilitic aortitis and aortic insufficiency was treated medically for ten weeks, but his condition became aggravated and life unbearable. The patient begged for the operation; it was done and the patient died several hours afterward. Postmortem examination showed an occlusion of the left coronary artery.

Those of the above operations, performed by Dr. E. G. Cutler, were, in each case, that of left cervical sympathectomy; in two cases excellent results were obtained. In one of these cases there were no results after two weeks; the pain returned, and the second operation on the

right side was done, cutting the superior cardiac nerve and the gray rami from the middle and superior ganglions. The patient slowly improved and in the end was relieved of the pain in his chest. There still remained throbbing in the axilla and pain in the upper arm.

Two operations extirpating the left superior and middle ganglions, one by Dr. Lilienthal and one by Dr. Newton, gave excellent results. After one operation by Dr. Newton, left superior cervical sympathectomy, there was at first an improvement and then the pain returned. A second operation of right cervical sympathectomy was done and the patient was considerably improved, and subsequent medical treatment has added to his improvement.

One operation of removal of the three left sympathetic ganglions and cord was performed by Dr. Cutler. Following this, the pain and constriction in the sternal region, on effort, were present for some months. This was easily relieved by nitroglycerine. These pains persisted for some months, but gradually grew less and for a year have not returned.

A patient with a syphilitic aortitis, mentioned as unsuccessful, was operated on by Dr. Cheever and the three sympathetic ganglia and their cord were removed. The patient, following the operation, was free from pain but was found dead in bed five hours after the operation.

In one unreported case of a patient who was a hopeless invalid from incessant attacks of anginal pain following the slightest exertion, an operation was done by Dr. Adrian V. Lambert, the sympathetic cord with its three ganglia and first thoracic being removed. The patient had a stormy convalescence with incessant attacks of pain and spasm in the left trapezius muscle, but the anginal pains did not recur after the operation. Three and a half years later anginal pains have not returned. At present, there is at times a marked tachycardia following sudden exertion and there is atrophy of the upper portion of the left trapezius muscle with limitation of movement of the left arm above the level of the shoulder. The patient, however, has gone back to her vocation of nursing, and instead of being a helpless invalid, is self-supporting.

It is evident, therefore, from the various operations performed, that different procedures may be equally successful when cutting different portions of the vegetative nervous system. The same procedure is, however, not successful in all individuals. It is evident, therefore, that, in all probability, the visceral afferent fibers from the heart vary in their tracts in man.

In animals the depressor nerve contains pressor as well as depressor fibers running to the medulla. As we have said, all painful stimuli of the afferent nerves, with the exception of the depressor nerve, produce a vasoconstrictor action through pressor excitation.

Wenckebach gives as a possible explanation of the occurrence of angina, that under certain pathological conditions, the depressor reflexes causing the vasodilation may be reversed into pressor reflexes, causing vasoconstriction and a rise of blood pressure. This reversal actually occurs with strychnine under certain conditions. Sherrington found that strychnine converted the fall of blood pressure produced by the depressor nerve into a rise. Strychnine also converts the reflex causing flexion of the knee joint, which is produced by contraction of the flexors together with the inhibition of extensors, into simultaneous contraction of both antagonists. Sherrington also has shown that tetanus toxin reverses inhibition to excitation in the case of the skeletal muscles. It is not impossible, therefore, that under certain pathological conditions in angina pectoris, there may be a reversal of the depressor action, with its defensive vasodilation and inhibition of the constrictors, into a vasoconstrictor action with an abnormal rise of blood pressure.

Removal of the superior sympathetic ganglion, or cutting the sympathetic cord below the ganglion, combined with section of the superior cardiac nerve, surely inhibits all pressor action of the fibers going up through these tracts. Cutting of the sympathetic cord, however, would be as effective as removal of the ganglion. If the ganglion is removed, it obliterates all the physiological action of the gray rami going out from its ganglion cells to the cervical nerves, and upward on the blood vessels to the gasserian ganglion, and to the cranial nerves. It is worth considering whether or not it is sufficient to cut the cord and the superior nerve. This may well be a better operation than that of obliterating the ganglions, since the object sought is the elimination of the pathway of the sensory nerves and the pressor reflex upward, and this is obtained by section of the fibers. Section of the depressor nerve seems also to have been successful either because it has counteracted the pathological change of the depressor into pressor effect, or because it has eliminated certain afferent and pressor stimulation going up in that nerve. It seems paradoxical to cut the depressor fibers, leaving only the afferent paths of pressor reflexes present, thereby obliterating the defensive and seemingly valuable reflex of vasodilation which prevents the abnormal rise of blood pressure in angina; but such operations have brought about the cessation of the anginal pain, which is the object sought in these patients.

Danielopolu is right in criticizing the removal of the first thoracic or inferior sympathetic ganglions. They are the pathway through which the accelerator fibers of the heart go, and these should be allowed to remain. Breaking the reflex arc does not cure the underlying pathological processes which cause angina, but one is justified in relieving the pain, even if the patient must die from the uncontrolled cardiac lesion; at least he dies painlessly, instead of in agony. To avoid re-

moval of such valuable nerve centers as the superior sympathetic ganglions, would seem to be the part of wisdom if the object in view can be otherwise obtained. Cutting the sympathetic trunks is therefore to be preferred. Operation is inadvisable in patients in whom the intense pain is caused by coronary disease, as they are poor surgical risks. It is therefore better to use the system of blocking off the painful impulses by injection of alcohol into the posterior root ganglions in the dorsal region, in the segments corresponding to the painful reflexes. If in aortic disease the reflexes occur in the cervical region, this procedure may well be tried before an operation, if the patient is a poor surgical risk. In this way, there is a greater probability of a comfortable prolongation of life than there is by surgical procedure. The blocking of the posterior root may be used in any case, if for any reason a surgical procedure seems inadvisable; or even if surgical procedure is advisable, blocking may be used first, and if inadequate there still remains the operation for relief.

In one of Danielopolu's patients it is interesting to note that when the pain had been blocked off, the sensation of extrasystoles, and the angor animi with fear of death still remained, although the anginal pain itself had entirely ceased.

SOME OBSERVATIONS ON THE EFFECT OF PITUITARY EXTRACTS UPON MAMMALIAN CORONARY VESSELS AND CARDIAC MUSCLE*

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IN STUDYING the effect of pituitary extract upon the heart three types of experiments are commonly employed. They are those in which the extract is injected intravenously into the animal, those in which strips of the coronary vessel are excised and exposed to baths of varying dilutions of pituitary substances and those in which the coronary vessels are cannulated, perfused and the extract injected into the perfusate. Considerable differences of opinion are found in the literature as to the effect of the extract. However, in most instances the experimenters failed to take into consideration the degree of acidity of either the fluid to which the heart was exposed or of the injected pituitary substance as possible factors in the final result.

In 1895, Oliver and Schäfer[1] noted an increase in blood pressure, decrease in heart rate and an increase in the force of contraction after the injection of an extract of the hypophysis cerebri. These results were later confirmed by Howell,[2] Schäfer and Vincent,[3] Garnier and Thaon[4] and Wiggers.[5] Meyer,[6] using "Pituoglandol Roche," noted no change in the coronary flow in the intact animals, when it was injected intravenously. Three experiments were performed by Morawitz and Zahn[7] in which one dog and two cats were used, and in these they observed that the coronary flow did not increase proportionately with the increase in blood pressure, and in one case it decreased in rate. With the use of the electrocardiogram a number of investigators[8] have found the conduction time of the impulse in the heart to be increased after the injection of pituitrin.

De Bonis and Susanna[9] studied the effect of fresh pituitary extract upon excised strips of ox coronary and noted contraction in every case. Similar results were obtained by Pal[10] with pituitrin (PD&Co).

In 1898 Hedbom[11] perfused the hearts of cats and rabbits and obtained increased tonus of the heart with a decrease in rate of coronary perfusion flow upon the injection of fresh aqueous extract on the hypophysis cerebri into the perfusate. Similar observations were made by Cleghorn,[12] Dale,[13] and Rabe.[14] Dale found pituitary extract to decrease the rate but increase the force of heart beat and that with the continued retardation of coronary flow the heart became weaker

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than before the injection. Rabe, using "Hypophysin" (BW&Co), noted increased heart rate and force, and in one case coronary vasodilatation. Recently Sumbal,[15] working with tortoises, showed that "infundin" (BW&Co) and "pituitrin" (PD&Co) produce dilatation of the coronary vessels. Because of these differences in results an attempt has been made here to determine if possible the true effect of some of the commercial and noncommercial preparations upon the coronary vessels.

METHOD

The experimental animals used were cats, rabbits and rats. The hearts were excised under ether anesthesia or after cerebral concussion and exsanguination. The perfusion fluid was either Locke's solution or Ringer's solution (P_H 7.6 to 7.8) to which in some cases autogenous defibrinated blood was added. The solution was kept at a constant temperature of 38.5° C. The method of perfusion was essentially the same as that used by Sherrington and Sowton[16] in perfusing the heart, with such minor changes as previously reported.[17] The free end of the arterial cannula was connected to a short rubber tube leading from a reservoir containing the perfusate. The perfusion pressure varied from 45 to 90 mm. of mercury but was uniform throughout each experiment.

The heart was perfused by inserting a cannula in the aorta near the origin of the coronaries. Dale[13] found this method sufficiently accurate with small hearts such as were used in these experiments. Free drainage of the heart was insured at all times by having it held with its apex upward. The apex was connected by a ligature to a myograph, thus recording the changes in cardiac activity on the kymograph surface. The perfusion fluid to the heart ran through a cannula fused in the side of a 100 c.c. Pyrex beaker inverted over a funnel which in turn collected the perfusion fluid leaving the heart. The drops fell on the lever of a receiving tambour connected to a recording tambour which recorded the rate of perfusion on the kymograph. In the top of the beaker a small opening was made to permit free passage of the ligature from the apex of the heart to the myograph.

The preparations of pituitary extracts used were "infundin" (BW&Co), "pituitrin O. and S." (PD&Co), "pituitol S. and O." (Wilson), "pituoglandol" (Roché), "pituitary solution S" (Squibb), "pituitary extract" (Inter. Prod. Co.), "pituitary solution full strength" (Abbott), "pituitary" (Swan-Myers), and extract of pure pituitary powder (Dr. Maurice Smith[18]).

The solid preparation dissolved in a small quantity of the perfusion mixture, and the liquid preparations usually undiluted and always at the same temperature as the perfusion fluid, were injected into the

perfusate near the arterial cannula against the perfusion fluid flow. Such injections had no lasting effect upon the perfusion pressure as this was quickly equalized by the escape of oxygen through the mercury valve. In some cases the commercial preparation was neutralized by the addition of N/10 NaOH with phenol red as the indicator.

A chronograph marking either five or fifteen second intervals was placed at the zero pressure level of the perfusion fluid. Unless otherwise stated all writing points were placed one above the other.

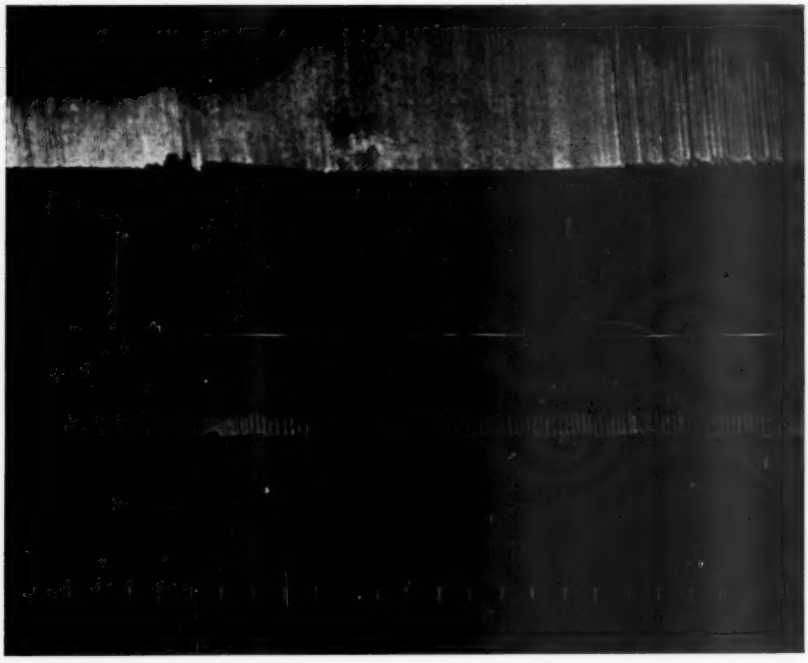

Fig. 1.—Active excised cat's heart perfused with Locke's solution P_H 7.6. Perfusion pressure 84 mm. of mercury. Top record heart beat, below it the perfusion pressure. Bottom record, point of injection and zero perfusion pressure, above it the time interval in five seconds. Middle record the perfusion rate in drops. At the point indicated in the record 1 c.c. of extract of pure pituitary powder (M.S.) 1 c.c. = 2.5 mg. was injected into the perfusate.

RESULTS

Pure Pituitary Substance.—My results confirm Dale's[13] findings. In most cases in which the heart was active decreased rate, increased force of beat and decreased coronary flow were noted after the injection. (See Table I and Figs. 1 and 2.) In Fig. 1, 10 mg. pure pituitary powder was dissolved in 4 c.c. of Ringer's solution (P_H 7.6), filtered and 1 c.c. was injected into the perfusate at the point indicated in the record. As a result of the injection the amplitude of the heart beat increased 100 per cent and the coronary flow decreased from 13 to 9 drops per ten seconds. In this instance the heart rate

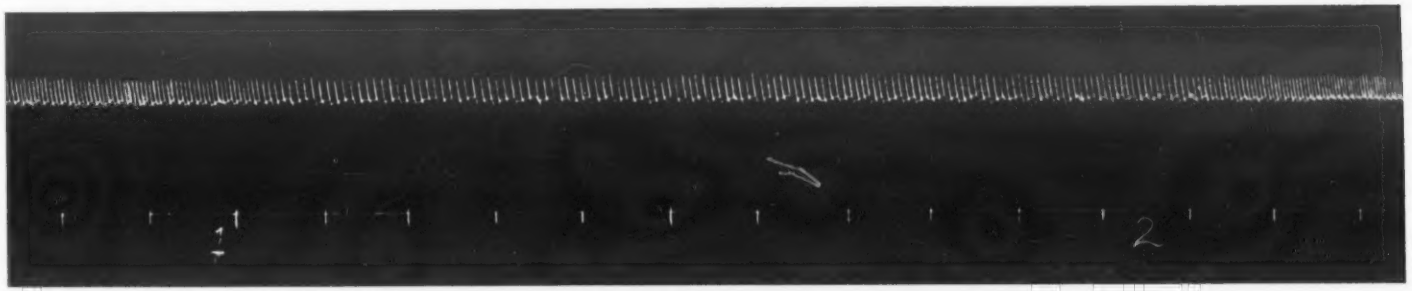

Fig. 2.

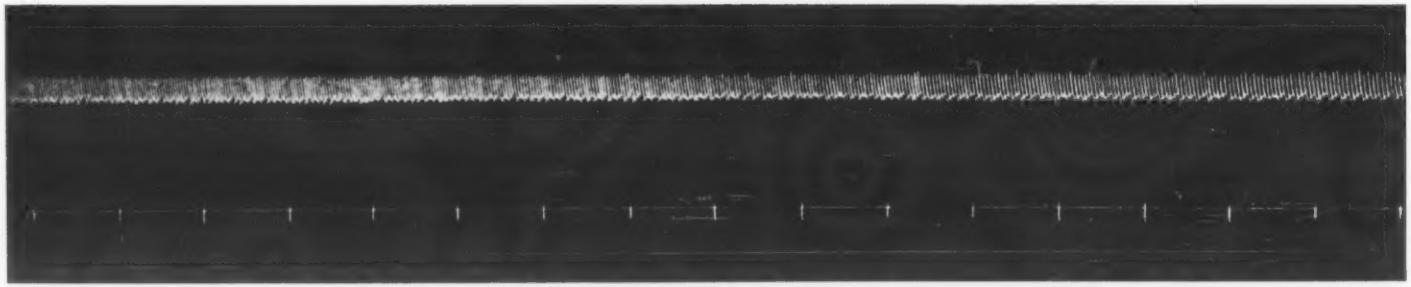

Fig. 2.—(Continued)

Fig. 2.—Excised inactive rabbit's heart perfused with Locke's solution PH 7.6 modified by the addition of autogenous defibrinated blood. Top record, perfusion rate in drops below it the time interval in fifteen seconds. Bottom record the time of injection.
1. Extract of pure pituitary powder (M.S.) (1 c.c. = 2.5 mg. of powder) 1 c.c. injected into the perfusate.
2. "Infundin" (BW&Co.) 0.5 c.c. injected into the perfusate.

increased from 19 to 24 contractions per ten seconds but in most cases it was diminished. In Fig. 2, at *1*, a similar decrease in the coronary flow is noted in an inactive rabbit's heart. The perfusate was a Locke's solution modified by the addition of autogenous defibrinated blood and the quantity of pituitrin was the same as that injected in Fig. 1. The rate of the perfusion flow before the injection was 20 drops, after the injection it was 12 drops per fifteen seconds.

Commercial Pituitary Extracts.—When the commercial pituitary preparations were used the opposite effects were observed. In all

Fig. 3.—Perfused excised active kitten's heart. Locke's solution P_H 7.6 to which autogenous defibrinated blood was added. Perfusion pressure 70 mm. mercury. Top record contraction of ventricles, below it the perfusion pressure. Bottom record, the time interval in fifteen seconds and zero blood pressure and above it the point of injection of drug. Middle record the perfusion flow in drops. At the point indicated in the record 1 c.c. "pituitol" was injected into the perfusate.

cases concentrated solutions injected into the perfusate decreased the height of muscular contraction, and in most instances, though the results were somewhat variable, the rate was also diminished. This can be seen in Fig. 3. In this case a kitten's heart was perfused with blood Locke's solution (P_H 7.6 to 7.8). At the point indicated 1 c.c. "pituitol" was injected into the persuate. There resulted a marked increase in the coronary flow with an accompanying decrease in force and rate of ventricular contraction.

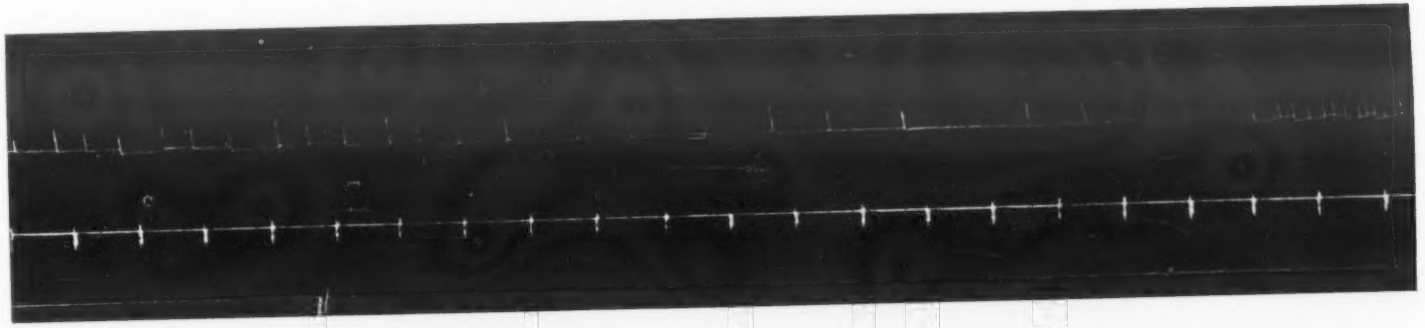

Fig. 4.

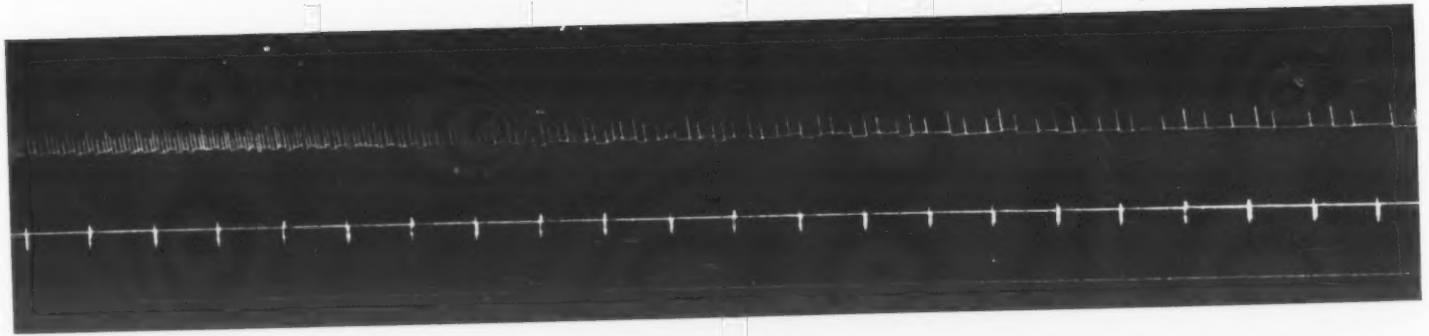

Fig. 4.—(Continued)

Fig. 4.—Excised inactive rabbit's heart. Blood Locke's solution Pʜ 7.6. Top record that of the perfusion rate in drops middle record the time interval in fifteen seconds and bottom record the time of injection of the 0.5 c.c. "pituitary solution" (Squibb).

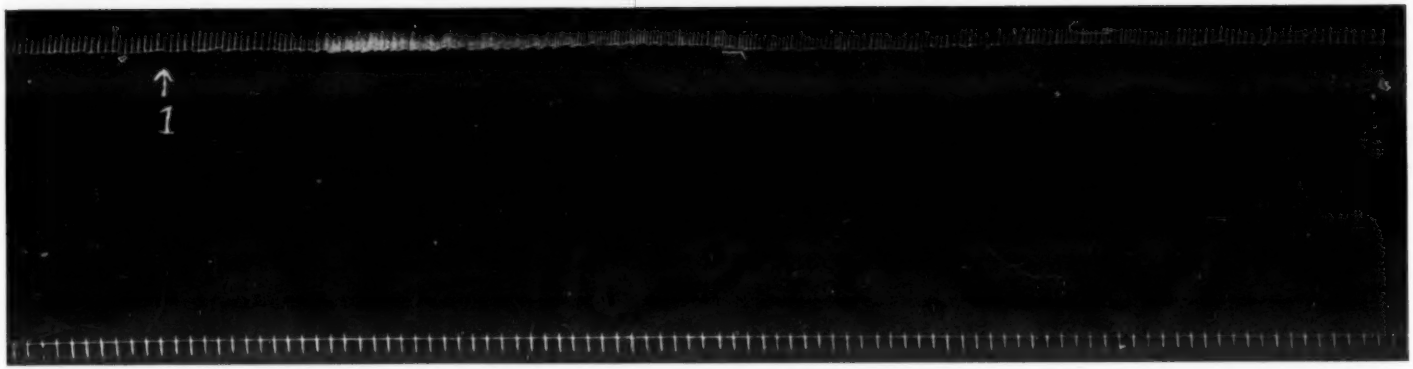

Fig. 5.—Excised inactive rabbit's heart perfused with Ringer's solution PH 7.6. Perfusion pressure 57 mm. mercury. Top record the rate of perfusion flow in drops. Bottom record the time interval in fifteen seconds and zero perfusion pressure. Middle record the perfusion pressure in mm. mercury 1. 1.5 c.c. N/10 HCl injected into the perfusate.

TABLE I

A table showing the effects upon the mammalian excised perfused coronary arteries, of commercial pituitary preparations compared with those of the extract of pure pituitary substance and of commercial preparations after neutralization. The perfusion fluid was either Locke's solution or Ringer's solution having a P_H of 7.6 to 7.8 and a temperature of 38.5° C. The perfusion pressure varied from 40 to 100 mm. of mercury but was constant for each experiment. Hearts of rabbits,* cats† and rats were used.

PREPARATION	QUANTITY INJECTED IN C.C.	RATE OF CORONARY FLOW IN DROPS PER 30 SECONDS	
		CONTROL	MAXIMUM CHANGE AFTER INJECTION
Infundin (Burroughs Wellcome & Co.) 93135	0.5*	86	194
	0.5*	62	144
	0.5*	50	126
	1.0	10	16
	0.5	28	62
	0.5	12	14
	0.5	13	22
	0.5†	6	10
	0.5†	20	36
	0.5*	12	34
	0.5†	20	38
	1.0*	18	108
	0.5	5	8
	0.5	3	4
	0.5	20	58
Pituitrin O. (Parke, Davis & Co.)	0.5*	58	130
	0.5†	12	18
Pituitrin S. (Parke, Davis & Co.)	1.0*	34	108
	1.0	9	3
	1.0*	6	10
	0.5	11	16
	1.0	8	20
	1.0†	2	4
	1.0	4	8
Pituitol (Wilson) 4707	0.5*	104	100
	1.0*	72	76–66
	1.0*	22	92
Pituitol "O" (Wilson) 4404	1.0	8	15
Pituoglandol (Hoffmann-LaRoche & Co.)	1.0	52	70–30
	1.0*	30	56
Pituitary Extract (Squibb & Sons) 8602	1.0	3	1–31
	1.0	6	3
Pituitary Extract (Inter. Prod. Co.)	0.5*	40	40
	0.8*	36	36
Pituitary Solution FS (Abbott) 33110	1.0	2	27
Pituitary (Swan-Myers)	1.0	5	2.5
Dr. Maurice Smith Pure pituitary powder 1 c.c. = 2.5 mg. dry powder.	1.0*	16	4
	1.0	18	10
	1.0	38	22
	0.5	22	10
	1.0	15	9
	0.5†	28	18
	1.0*	18	12
	1.0	80	48
	1.0	28	18
Infundin + N/10 NaOH to neutralization. P_H 7.4–7.6	0.5	7	5
Pituitrin "S" + N/10 NaOH to neutralization. P_H 7.4–7.6 (Parke, Davis & Co.)	1.0	5	2.5
	0.5	10	30
	0.5	5	2
	0.5	3	1

Similar results were obtained with all commercial pituitary solutions tested. In Fig. 2 at *2*, 0.5 c.c. "infundin" was injected into the perfusate of an inactive rabbit's heart. The rate of perfusion flow quickly increased from 15 to 35 drops per fifteen seconds.

Occasionally commercial preparations cause a constriction of the coronaries before the dilatation. (See Table I and Fig. 4.) In this experiment an inactive rabbit's heart was perfused with Locke's solution (P_H 7.6) modified by the addition of autogenous defibrinated blood. At the point indicated in the record ½ c.c. of "pituitary solution" (Squibb) was injected into the perfusate. Two minutes later a decrease in the perfusion rate is observed and five minutes later the perfusion rate is more than eight times as fast as was the control rate. It appears, therefore, that we have present in the commercial preparation some coronary dilator substance. This vasodilator action of commercial pituitary extracts we believe to be caused by the acidity of the products used. Using phenol red as the indicator from 1.5 to 1.56 c.c. of N/10 NaOH were required to neutralize 1 c.c. of either "pituitrin" (PD&Co) or "infundin" (BW&Co). Such increases in acidity increase the coronary flow as can be seen in Fig. 5. Here an inactive rabbit's heart was perfused with Ringer's solution (P_H 7.6). At *1*, 1.5 c.c. of an N/10 HCl solution was injected into the perfusate. As a result the rate of flow increased from 9 to 25 drops per minute. Moreover when the P_H of the commercial pituitary preparations was increased to that of the perfusion fluid, these extracts were as effective in producing vasoconstriction of the coronaries as was the pure pituitary solution made from pituitary powder.

Diluting the commercial preparations changed merely the degree of dilatation produced.

SUMMARY

1. Pure pituitary extract when injected into the perfusate causes an increase in the height of ventricular contraction with usually a decrease in rate. Occasionally the rate is also increased.

2. The coronary flow is decreased upon the addition either of pituitary extract or of most commercial pituitary extracts neutralized to the perfusate. In our experiments vasodilatation of the coronaries occasionally persisted after neutralization of those commercial preparations in which chloretone was present as a preservative.

3. All commercial pituitary preparations tested produced dilatation of the coronary vessels. This vasodilatation is probably due to the acidity of the solution and not to an active vasodilator substance in the preparations.

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FURTHER STUDIES ON CONDUCTION IN THE HIS BUNDLE*

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IN RECENT years a number of new theories have been advanced to explain the abnormal prolongation of time interval between the auricular and ventricular contraction. Straub,[1] from an analysis of a clinical curve, concluded that the excitation wave travels rapidly and undisturbed through the whole conduction system, and that an increased latency of the ventricular musculature alone is responsible for the lengthened P-R interval.

From their experimental studies both Hering[2] and Lewis[3] believed this phenomenon to be the result of a conduction disturbance in the atrioventricular nodal tissue only, the bundle itself taking no part in the disturbance.

Mobitz[4] also, finding support in theoretical considerations of clinical electrocardiograms, advocated the theory that the cause of the prolongation of the normal auriculoventricular interval lay in the A-V nodal tissue. His conception differed, however, from that of Hering and Lewis in that it assumed an increased latency of the A-V node, rather than a disturbed conduction through this tissue. Mobitz believes, as the above investigators do, that the conduction through the bundle of His is undisturbed.

In all these theories it is supposed either that the latency or conductivity of the upper part of the A-V connecting system (the Tawara node) is disturbed, or that the latency of the ventricular muscle itself is prolonged, while the system between these two points, i.e., the bundle, takes no part at all in the abnormal prolongation of the P-R interval.

The older teaching of Engelmann and Wenckebach,[5] however, is that the prolongation of the normal conduction time between auricular and ventricular contractions is due to delayed conduction in the muscle fibers of the whole or some part of the specific muscle tissue system. This delay depends upon the length of the rest and recovery time of the part involved.

In recent reports by us[6, 7] of experimental studies on conduction in the bundle and bundle branches, evidence has been presented to support the Wenckebach conception.

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With the present graphic methods of registration of the electrical variations accompanying the heart beat, the P-R interval can be measured as a whole only, and the differences in function of the various parts of the conduction system cannot be seen or measured.

Experimental studies on this part of the cardiac mechanism have been very difficult, for poisoning with drugs or by asphyxia impairs not only the part to be studied but the whole conduction system, and the rest of the cardiac musculature as well, while mechanical means such as the Erlanger or Meakins clamps, which squeeze and lacerate tissue and do not definitely localize the lesion (node or bundle), are too coarse for use in so small an area. Consequently results of experimental studies upon this portion of the cardiac tissue, in which such methods were used, have always been open to just criticism.

We decided to use nodal rhythm in our studies, for we then had a path from the acting pacemaker in the node to the auricle on the one hand, and to the ventricle on the other. Any conduction disturbance in either one of these paths would appear as a change in the P-R interval which could be easily measured and localized.

Auricular and ventricular extrasystoles were used to produce changes in the efficiency of one or the other of the above-described paths. This method caused disturbances in certain parts of the conduction system, while the rest of this system and the heart musculature itself, were left as nearly normal as possible.

We opened the thorax of dogs under morphine-ether anesthesia and artificial respiration, cut both vagi and the right accelerans. In some cases the preponderance of tonus of the left accelerans, under these conditions, was enough to cause nodal rhythm. In most cases, however, we clamped the sinus node to attain that end.

We studied the effect of ventricular and auricular extrasystoles in nodal rhythm, with the pacemaker either in the lower or in the upper part of the node.

It was found that when the point of origin of the impulse in a nodal rhythm was in the lower part of the node, and the P-wave was either buried in the ventricular complex or followed the R (negative P-R or R-P interval), a ventricular extrasystole would cause the P of the first post-extrasystolic A-V beat to appear before the R (positive P-R interval) and, in the succeeding beats, gradually to move back to its original position.

When the point of origin of the impulse was in the upper part of the node, that is, when there was a definitely positive P-R interval, a ventricular extrasystole would cause an effect exactly opposite to the above-described phenomenon. The P-wave disappeared in the ventricular complex of the first post-extrasystolic atrioventricular beat, and gradually reappeared in the following beats until it had again reached

its previous position. Both these phenomena appeared under analyzable conditions.

Auricular extrasystoles also were followed by these same phenomena.

That the activity of a new center for the auricle or for the ventricle, or the shifting of the pacemaker in the A-V node itself, could not explain these findings we saw upon analysis of our cardiograms. The auricular rate was practically unchanged, the P-P distances always being equal. The auricular rhythm was changed only when a ventricular extrasystole was retrogradely conducted to the auricle, or when auricular extrasystoles occurred.

The interventricular periods, however, showed very definite changes in time relation.

We found that the cause of the changing relationship of the P-wave to the ventricle complex in our curves was due to a disturbed conduction from the pacemaker in the A-V node to the ventricle. In the first instance when the pacemaker was in a lower part of the node the positive P-R interval of the first post-extrasystolic A-V beat was caused by a prolonged conduction from the lower part of the node to the ventricle. The post-extrasystolic pause was *overcompensatory*. The A-V rhythm as expressed by the auricular rate (the conduction from the pacemaker to the auricle not having been disturbed) being unchanged, it would be necessary then, if our conception is correct, for the ventricular periods following the first post-extrasystolic period to be just so much shorter as the first post-extrasystolic period was longer. This change in the interventricular periods is exactly what we found.

In the second series where the pacemaker was in the upper part of the node, the disappearance of the P-wave in the first post-extrasystolic beat was caused by better conduction through the bundle. Here again the measurements of the interventricular periods spoke for our explanation. The first post-extrasystolic pause was shorter. It was *undercompensatory* and the following periods were longer and gradually became shorter until their normal length was reached. (R-R distance before the extrasystole.)

We found the same definite rules after auricular extrasystoles, and in addition we saw that the more slowly the auricular extrasystole was conducted from the node to the ventricle, the earlier the auricular contraction of the first post-extrasystolic atrioventricular beat came after the extrasystolic ventricular contraction. As the P-R distance of the auricular extrasystole was increased, the following R-P distance was decreased. These constant findings can be explained only by assuming that the conduction in tissue lying below the point of origin of the impulse has been disturbed.

If the P-R interval of the extrasystolic impulse were prolonged because of either an increased latency of the Tawara node (Mobitz) or impaired conduction through the nodal tissue only (Hering, Lewis),

the formation of a new atrioventricular impulse would begin immediately before the ventricular contraction of the auricular extrasystole, just after the impulse leaves the node, and the above-described shortening of the post-extrasystolic R-P interval would be impossible. As it is, the new A-V impulse is being formed in the node while the previous extrasystolic impulse is delayed in its course through the bundle.

In our previous experiments we also showed cardiograms which indicate that the appearance of our phenomena was entirely independent of the length of the preceding ventricular diastole, which alone would determine the increased or decreased latency of the ventricular musculature. (Straub.)

It would seem then that our curves can best be explained upon the basis of length of the rest and recovery time of the bundle and other tissue below the point of origin of the impulse in the A-V node, the prolonged conduction time from the pacemaker in the node to the ventricle being dependent upon a shorter rest and recovery time (the appearance of a definite P-R interval in the first post-extrasystolic beat) and the disappearance of the P-wave in the post-extrasystolic ventricular complex being due to a better conductibility of the bundle and tissue below the pacemaker as the result of a longer rest and recovery time.

We had brought evidence to support Wenckebach in his theory that the rest and recovery time of the whole or any part of the A-V connecting system, rather than the latency of the node, conduction disturbance through the nodal tissue, or the latency of the ventricular musculature, is the cause of the abnormal prolongation of the P-R interval. Many curves hitherto described as "wandering of the pacemaker," "sinus escape" and some cases of interference dissociation (Mobitz),[9] can better be explained by conduction disturbances in the bundle.

In the endeavor to prove that all parts of the specific tissue are subject to the same conduction disturbances as the A-V connecting system we[7] studied conduction in the bundle branches.

Using the same methods as in our previous experiments, i.e., nodal rhythm, etc., we cut one of the bundle branches at about the junction of its upper and middle thirds, and after recording this result, we pressed lightly with the back of a small knife upon the intact bundle branch. At first we recorded complete block curves, and later during the recovery period of the so damaged uncut bundle branch, we recorded all types of partial block, i.e., simple prolongation of the P-R interval with and without dropped beats (Type I), and also dropped beats without any change in the P-R interval (Type II).

We saw, therefore, that a direct mechanical impairment placed at will, without the Tawara node coming into consideration at all,

caused all those forms of conduction disturbances in the bundle branches which we were accustomed to seeing in the A-V connecting system.

The experiments showed also that Type I of conduction disturbance, considered by Mobitz[4] to be a result of functional disturbance, can, as well as Type II, be caused by anatomical-pathological disarrangements, both these types being caused in our experiments by the same experimental methods.

During the course of other experimental studies we repeatedly obtained curves that could be analyzed in the sense of our previously

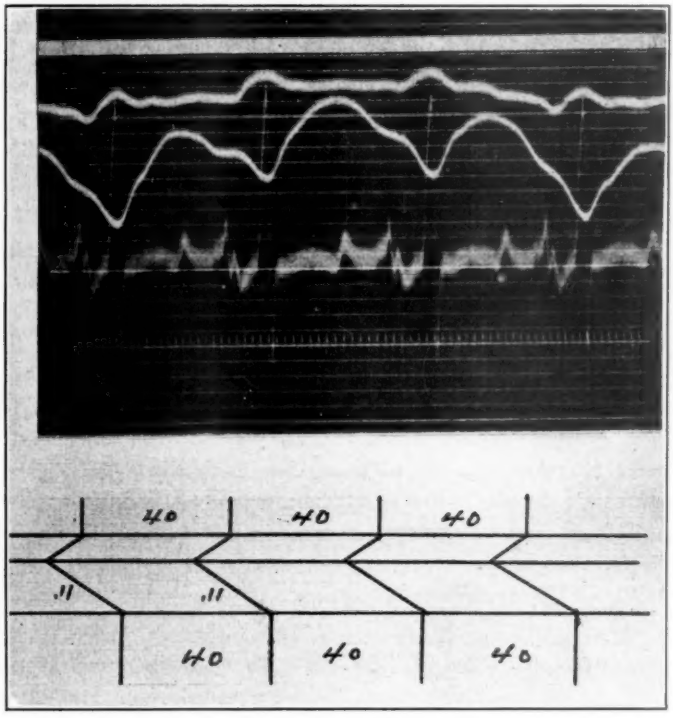

Fig. 1.—Cardiogram of a dog. Both vagi and right accelerans cut and sinus node clamped off. Nodal rhythm with the pacemaker in the upper part of the A-V node. P-R = 0.11 sec. P-wave diphasic mainly positive. A-V rate = 150.

reported studies, and the curves published below are examples of such records taken under varied conditions.

Dogs were used under morphine-ether anesthesia. Both vagi and the right accelerans were cut, and the sinus node was definitely clamped off, nodal rhythm resulting. We recorded the ano-esophageal lead only. The right auricle and the conus of the right ventricle were suspended for mechanical registration.

In our curves the uppermost line is for the recording of make-and-break galvanic impulses. The curve beneath this is the mechanical

registration of the auricular contraction, below that the mechanical registration of the ventricle and below that the cardiogram. The bottom line is the timemaker, each division being one-fiftieth of a second.

Fig. 1 is a curve taken under the above-mentioned conditions. The A-V rate is 150. We have a positive P-R distance of 0.11 sec. The P-waves are diphasic, with a higher positive than negative movement. They are in the main positive. The pacemaker seems to be in the upper part of the node. Ventricular complexes are normal.

Fig. 2 is a curve taken during the same experiment, while the right vagus was being stimulated by a very weak faradic current. The A-V nodal rate is now 71. The P-R intervals before the extrasystolic contractions are 0.19 and 0.20 sec. The P-waves in this curve differ from those in Fig. 1 only in that they are broader. The form of the P-waves after the extrasystole remains unchanged although their relationship to the ventricular complex changes considerably.

The first of the two ventricular extrasystoles is electrically provoked, and the second is spontaneous. Neither of them disturbs the auricular rate. They are not conducted up to the A-V node. E^1 is premature by only 0.07 sec. and E^2 follows 0.41 sec. later. Complex 5 differs from the other complexes. The P-wave, which as we have previously stated, has exactly the same form as the preceding P-waves, now follows the ventricular complex. It is sandwiched in between the end of the S and the beginning of the T-waves. The ventricular complex has a very slightly changed form because of the presence of the P in it. In complexes 6, 7, and 8 the relationship is again reversed, and the P-R distance gradually enlarges until it is the same as P^2-R^2.

The ventricular rate, unlike the auricular rate, which shows practically no changes, is very definitely disturbed.* In the first place the post-extrasystolic pause is undercompensatory and the following R-R intervals are larger and gradually become smaller until they reach about the normal distance.

The diagram of Fig. 2 explains our conception of the mechanism. We have nodal rhythm with the pacemaker in the upper part of the node. E^1 is 0.07 sec. premature and its retrograde impulse strikes the bundle when the A-V impulse of this same complex 3 has almost reached the ventricle. E^2 which is only 0.41 sec. later reaches the bundle after it has had only a very short rest and recovery time, and both the retrograde impulse from E^2 and the A-V impulse of complex 4 do not advance very far. The next A-V complex 5, however, finds the bundle in such good condition, because of a long rest and recovery time, that it conducts the A-V nodal impulse of that

*It must be taken into consideration that the apparent slight changes in the auricular and ventricular rate are due to vagal stimulation. Wenckebach[8] thinks that only a bradycardia that shows irregularities in rate may be ascribed to vagal influence.

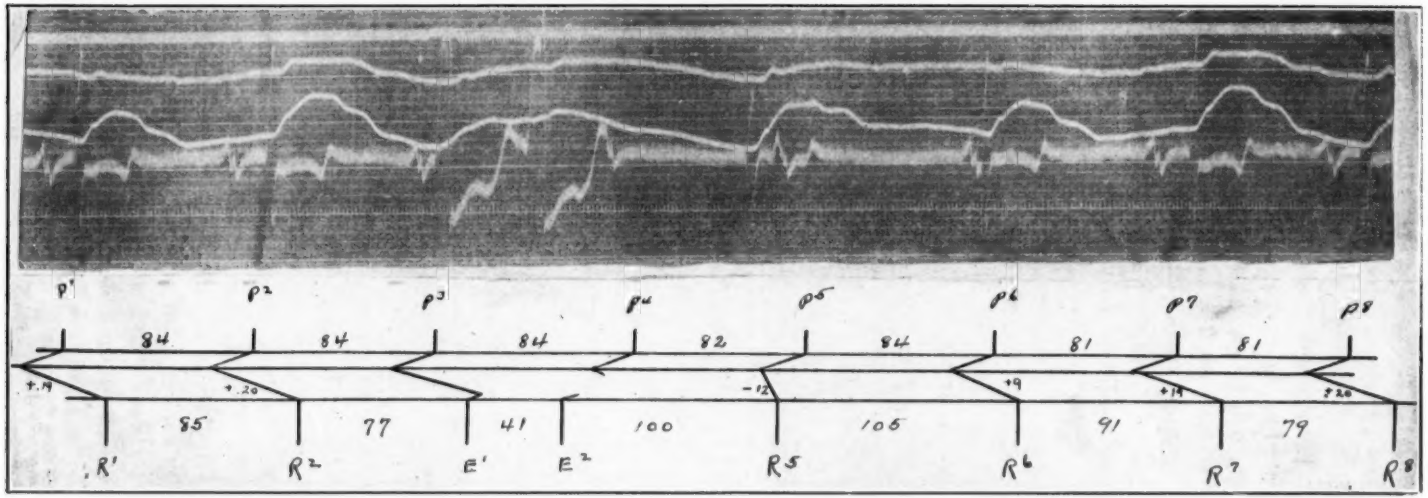

Fig. 2.—Cardiogram (during the same experiment in which Fig. 1. was obtained) after weak faradic stimulation of right vagus P-R 20 sec. in complexes preceding the extrasystoles. P-waves wider than in Fig. 1. A-V rate = 71. Notice the change in relationship of the P-waves to the ventricular complexes after the extrasystoles.

complex to the ventricle in so short a time (the conduction time from the node to the auricle not being disturbed), that the ventricular portion of the complex is seen before the auricular. The gradually increasing length of the P-R intervals of the following complexes depend upon a gradual decrease in the rest and recovery time of that portion of the conduction system.

Complex 5 is not an A-V escape nor is it caused by a shifting of the pacemaker in the node. In the first place the sinus was completely clamped off and a comparison of our curves before and after the sinus clamping showed us definitely that the function of the sinus had been taken over by another pacemaker. In the second place there could not have been a change of position of the pacemaker in the node itself because there was no change in the A-V rate, and no change in the shape of the auricular complexes.

Now the question arises as to whether we are really dealing with a nodal rhythm in these curves. We have a positive P and a positive P-R distance. Mobitz[9] and Schellong[10] believe it is necessary to have a negative P-wave to make certain the diagnosis of nodal rhythm in clinical curves, while Edens[11] and others have described clinical cases of nodal rhythm with positive P-waves.

Our interest, however, is centered upon the diagnosis of nodal rhythm in experimental records, and on this point we encounter many divergent opinions. Ganter and Zahn[12] believe that a positive P denotes in all cases that the impulse arises in the sinus node, while a negative and a diphasic P with the first part negative speaks for the impulse rising in the A-V node. Williams and James[13] Rothberger, Winterberg, Lewis, White and Meakins, Hering, and many others have observed positive P-waves in undoubted nodal rhythm in experimental studies.

Eyster and Meek[14] arrived at the conclusion that the determination of the primary negativity of the nodal region was really the only way definitely to prove nodal rhythm.

In our previously reported experiments we came to the conclusion that the presence of the phenomena that we described, that is, the disappearance of the P in the post-extrasystolic complex in cases where there was a R-P interval, and the appearance of a P-wave in the post-extrasystolic complex when previously the P had been lost in the ventricular complex after extrasystoles, ventricular or auricular, was proof that we were dealing with nodal rhythm despite a positive P or a definite P-R interval.

We see in this curve Fig. 2, therefore, the same conditions that were described in our experiments when, during nodal rhythm with the pacemaker in the upper part of the node, an extrasystolic contraction caused:

1. The displacement of the P-wave behind the ventricular contraction in the first post-extrasystolic A-V complex.
2. The unchanged auricular rate.
3. The unchanged form of the P-waves following the extrasystoles.
4. The undercompensatory post-extrasystolic pause.
5. The definite changes in the interventricular distances.

This curve is therefore one of nodal rhythm, with conduction disturbances (in that part of the conduction system between the pacemaker in the node and the ventricle) because of a longer or shorter

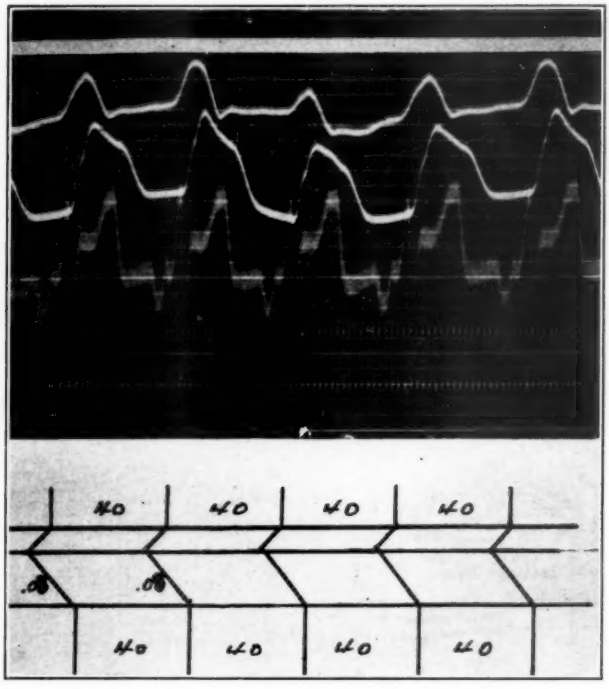

Fig. 3.—Cardiogram, dog, vagi and right accelerans cut, S-A node clamped, and right bundle branch cut. Nodal rhythm. P-R = 0.08 sec. P-waves inverted. A-V rate = 150. Right bundle-branch block.

rest and recovery time; or in other words because of the greater or lesser demand put upon it, per time unit, by ventricular extrasystoles.

Incidentally in one portion of this curve we see a much better conduction time after a diastole of 0.1 sec. (E^2-R^5) than after a diastole of 0.105 sec. (R^5-R^6), showing that the length of the diastole alone does not always influence the length of the following P-R interval, as it would be necessary to believe if the latency of the ventricular musculature were the cause of the change in the P-R interval.

Fig. 3 is a curve from an experiment on a dog under morphine-ether anesthesia and artificial respiration. Both vagi and right accel-

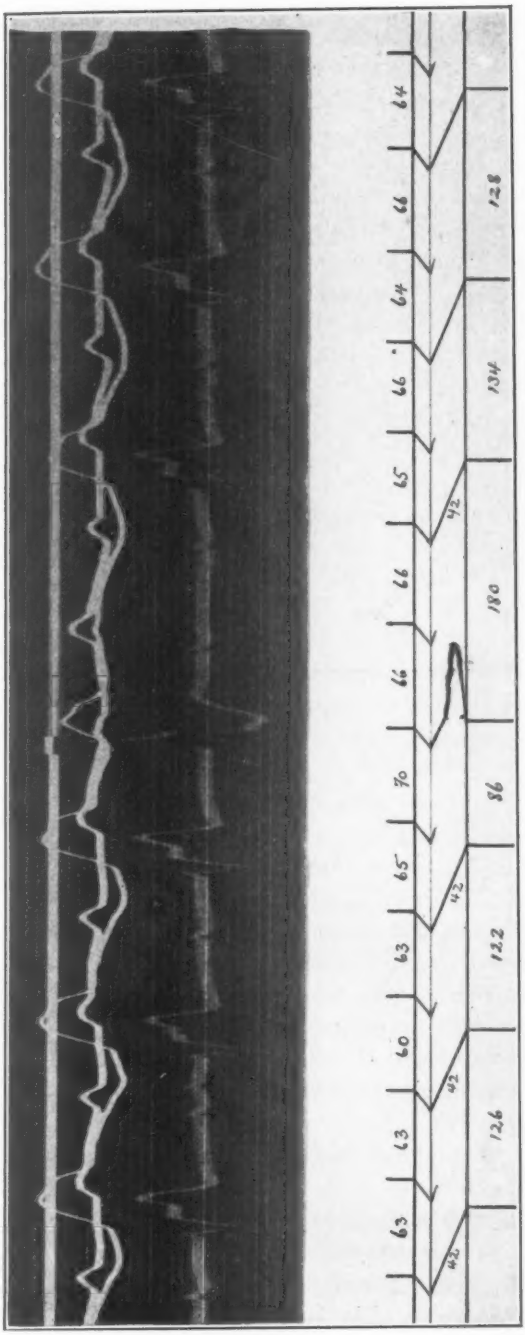

Fig. 4.—Cardiogram (from experiment in which Fig. 3 was obtained). The intact left bundle branch was pressed upon with the dull side of a small knife and this curve was taken during its recovery, after a period of complete block. We have, therefore, complete right bundle block, partial left bundle-branch block (Type I) and nodal rhythm. P-R is now 42 sec. and every other beat is dropped. The P-R intervals following the vent. extrasystole are the same length as those preceding it. (See text.)

erans were cut, and the sinoauricular node was clamped off. The right bundle branch was cut.

The rate is 150 and regular. The P-R interval 0.08 sec. P-waves are negative and the ventricular complexes are those of right bundle-branch block. The point of origin of the impulse is in the upper part of the node.

Fig. 4 is a curve from the same experiment. The left bundle branch, which was intact, has been pressed upon lightly by the back of a very small knife, and this curve was taken during the recovery time of the left bundle after a period of complete block. We see, therefore, the same nodal rhythm as in Fig. 3. The P-waves, however, are now positive. The P-R interval is 0.42 sec. and only every other impulse is conducted. We have therefore nodal rhythm, complete right bundle-branch block, and Type I of partial block with dropped beats in the left bundle-branch.

The interesting point to be explained in this curve is why, after a diastolic period of 1.80 sec., the P-R interval of the post-extrasystolic complex still remains the same length as the P-R intervals of the conducted beats before the extrasystole. Acording to Straub this P-R interval should be shorter, for after so long a diastole, the ventricular muscle latency should certainly have been shorter. According to our conception it would depend entirely upon the rest and recovery time of the part of the conduction system involved. The electrically provoked ventricular extrasystole strikes the bundle in its lower part after a very short rest and recovery period, for it comes only 0.86 sec. after the last nodal ventricular contraction. The upper part of the system between the pacemaker in the node and the ventricle is conducting the A-V impulse at the same rate as the previous A-V impulses are conducted, but it comes to a part of the bundle that has already been called upon by the demands of the retrograde impulse from the ventricular extrasystole and it does not go any further. The next A-V impulse is conducted to the auricle, but the lower part is now in no condition to conduct an impulse, and it is therefore blocked. The refractory period of the ventricle does not play any part in the nonconduction of this impulse because when the impulse, at the rate that it traveled, had reached the ventricle, it would have been out of the refractory period of the preceding ventricular systole. The first post-extrasystolic ventricular impulse is conducted in the same time as the previously conducted nodal impulses because, by the meeting of the retrograde impulse from the ventricular extrasystole with the nodal impulse, at the time it does, the bundle is given the same rest and recovery time as the previous complexes have had.

This curve, therefore, is of interest because it shows:

1. A prolonged P-R interval with dropped beats due entirely to a conduction disturbance made by the pressure of the back of a small

knife passed over one of the bundle branches, the nodal tissue not being at all involved.

2. That the rest and recovery time of any part of the specific system influences the speed with which it conducts its impulses.

3. That Straub's conception of the prolongation of the P-R interval is not tenable, because we show very definitely no change in the P-R interval after a very long diastole.

SUMMARY

Résumé of previously reported experimental studies upon conduction in the A-V bundle and bundle branches which show that:

1. In nodal rhythm, with the P-waves buried in the ventricular complexes (pacemaker in the lower part of the node) a ventricular or auricular extrasystole, under certain conditions, will cause a positive P-R interval in the first post-extrasystolic A-V complex, the P-wave gradually moving back to its original position in the following complexes.

2. In nodal rhythm with positive P-R intervals (pacemaker in upper part of node) a ventricular or auricular extrasystole, under certain conditions, will cause the P-wave of the first post-extrasystole A-V beat to be buried in the ventricular part of that complex and gradually to move back to its original position in the following complexes.

3. The cause of these phenomena, we believe, is an altered conductivity of the specific tissue lying below the point of origin of the impulse, caused by a lengthened or shortened rest and recovery time of that tissue. We therefore bring evidence to support the Engelmann and Wenckebach conception of the cause of the pathological prolongation of the P-R interval.

4. Neither "shifting of the pacemaker" nor "sinus escape" can explain these findings.

5. In our studies on conduction in the bundle branches, when one branch was cut and the other one pressed upon with the dull side of a small knife, we obtained curves showing all forms and degrees of complete and partial A-V block.

6. We can have conduction disturbances in the bundle branches giving us the above curves, without the A-V node or the ventricular musculature coming at all into consideration.

7. Curves of Type I of partial block (gradual lengthening P-R interval with dropped beats) were produced by anatomical lesions. This fact rather argues against the impression of Mobitz that this type of block is due only to functional disturbances.

Cardiograms presented, examples of many obtained in the course of other experiments, are analyzed in the sense of our studies. They also tend to show:

1. In animal experiments, ano-esophageal lead, positive or diphasic P-waves can be seen in undoubted nodal rhythm.

2. Ventricular extrasystoles are conducted backward in the bundle and bundle branches for a greater or lesser distance, causing a greater demand upon that tissue, though they do not provoke an auricular contraction.

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POSTTRAUMATIC DISTURBANCES OF THE HEART*

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THE relative infrequency of cardiac wounds makes their occurrence always one of general interest and the unusual features accompanying such injuries have a distinct appeal to the fancy of all interested in the heart and its affections. No one would gainsay that cardiac trauma offers a field for academic speculation presented, perhaps, by no other organ of the body, not excepting the brain itself. From a purely cardiological point of view injuries to the heart present a rare opportunity to observe clinically in man what experimentally has been accomplished in laboratory animals. The close observation of all such cases may do much to knit more closely the results of clinical cardiovascular examinations with actual pathological physiology of the heart.

Such posttraumatic cardiovascular studies have not been numerous; Davenport[1] in 1924 was one of the first to publish a complete study with electrocardiographic tracings of a punctured wound of the heart which he had operated upon. Prior to this, the literature of heart injuries had been almost exclusively concerned with the surgical aspects of the problem. Davenport quotes Farina's operation upon the heart performed in Rome in 1896 as one of the earliest published accounts of successful surgery of the heart. Vaughan[2] collected 150 cases of repaired hearts in the literature up to 1909; Constantini[3] increased this number to 201 in 1919. Immediately thereafter as a result of the addition of war casualties, the number of heart injuries operated upon was increased by 501 cases, of which 260 rapidly had a fatal outcome.

The case herewith presented is of exceptional interest in that the exact site of the cardiac injury is known, as well as the type of "foreign body" which was buried in the myocardium. A preliminary report of this case has already been published by one of us,[4] but the removal of the patient to New York has made possible the subsequent cardiovascular observations of the case.

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*From the Witkin Foundation for the Study and Prevention of Heart Disease at the Beth David Hospital, New York.
Read before the Harlem Medical Association, May 5th, 1926.

CASE REPORT

A. L., negro laborer, aged twenty-four years, during an encounter with an associate, was stabbed with a long-bladed pocket knife on the evening of July 23, 1925. The external wound was approximately three inches long, extending from the third to the fifth ribs just within the left nipple; the costal cartilage of the fourth rib was entirely severed. When seen about forty-five minutes after the receipt of the injury, the patient was in extreme shock. Very little blood was coming from the wound, but the clothing was quite saturated. The pulse was occasionally palpable at the wrist; the skin was cold and damp. The patient was exceedingly restless and thirsty.

Under light ether anesthesia the wound was explored and it was found necessary to enlarge the external laceration in order to examine the damage which had been done deeper. An incision was made downward and to the right and then the flap was turned backward toward the sternum after removing portions of the fourth and fifth ribs. The pericardial sac was then nicely exposed; it was not distended, as the laceration was of sufficient size to permit the blood to escape into the chest cavity and through the chest wound. The pericardium was quickly opened and the heart was seen contracting at a delirious rate which could not be well counted. An epicardial wound was seen situated high up in the left ventricle not far from the anterior interventricular groove; not much blood was spurting from the wound, possibly because of the serious previous hemorrhage. A finger placed in the epicardial wound which was about 1½ inches long passed readily into the cavity of the left ventricle, the wound on the endocardial side being about 1 inch long.

As rapidly as possible the heart was brought up into the incision by grasping the cut edge of the myocardium with a towel forceps; this was done in order to steady the heart while the sutures were being inserted. Four interrupted sutures of medium silk were taken, the first one being double. The sutures were placed *in* the myocardium but not through into the ventricular cavity. About 1½ inches of silk were taken for each suture so that 7½ inches of suture material were buried within the wall of the left ventricle.

The pericardial sac was closed with a continuous running suture of chromicized catgut and the external wound with interrupted silkworm-gut sutures. The entire operative procedure was done with some difficulty as the left lung herniated through the incision with each respiration. No blood transfusion was attempted because all available donors were found to be incompatible. Salt solution had been given intravenously as the operation was being performed and when a suitable donor was found some time later, the patient's condition had considerably improved.

The patient reacted rather well. In two weeks he was permitted to sit up with a back rest. His pulse was running about 100; respirations 22; and temperature at 98.4°. Except for fleeting precordial pains, the patient did not complain of his injury. On the twentieth day he suddenly developed a right lower and middle lobar pneumonia and after a rather stormy process he made a slow convalescence. On September 13, nearly two months after receiving his injury he

Fig. 1.—Operative scar and rib-denuded area overlying heart.

was discharged from the Youngstown Hospital. His pulse rate had remained at 100, increasing to 120 on moderate exercise and returning to 102 after three minutes rest.

The heart at that time was of normal size, displaced toward the right, and lying directly in midline. There was an adhesive pericarditis with systolic retraction of the chest wall. The heart sounds had good muscular quality and no murmurs were heard.

On November 28, four months after the injury, his pulse had dropped to 78, increasing to 88 on exercise. He reported as feeling well without any specific complaints.

He was next seen in New York on March 16, 1926, about eight months after the injury. A brief résumé of a cardiovascular study made at that time at the Cardiac Clinic of the Witkin Foundation (No. 6-039) follows:

The patient is at his theoretical normal weight. Under the Dressler white light he presented no cyanosis of his mucous membranes. During the course of the examination he became somewhat dyspneic.

The chest appeared somewhat asymmetrical, the right side being larger than the left. The original laceration and the operative scar had nicely healed; the site of the operation was now represented by a triangular area having its base at the left sternal margin. This area measured about 7 cm. × 9 cm. × 11 cm. in size. The movements of the heart could be readily seen by their pulsation against the thin overlying skin (Fig. 1).

Palpation of the apex in this area was easily accomplished and the fingers could almost be passed around the lower part of the heart. When the apex was squeezed or pressed firmly, the patient would complain of a "sickish weakening" sensation, but no actual pain. He was unable to localize the origin of the feeling, but usually described it as arising "somewheres deep in the stomach"; occasionally it would be referred to the deeper portions of the left chest, generally in the front.

During the course of the observation a mishap occurred which was of considerable interest. The apex was percussed rather sharply and the patient immediately complained of excruciating pain in the left shoulder which persisted for some moments, and left him rather apprehensive of subsequent manipulation.

The heart did not appear enlarged to percussion, although it was definitely displaced into the right chest. The heart sounds were clearly heard over the entire precordium; the first and second sounds at the apex had about the same tonal qualities. At the base, the second aortic sound was much accentuated over the second pulmonic. All valve closures had a rather good tonal quality.

The dominant rhythm of the heart was regular; the apical rate was 96 beats per minute. All of the apical beats were transmitted through to the radial artery. A sinus arhythmia was readily demonstrated and other vagal effects like the Rehfisch breath-holding test and the ocular-cardiac reflex of Starling were positive. No murmurs or extra cardiac sounds were heard.

The right lung had essentially normal breathing throughout; on the left side, however, at the base there were many coarse moist râles

which did not disappear after coughing. All breath sounds were greatly increased. At the left apex, there was a rather large area extending downward to the spine of the scapula which had bronchial breathing. At the left base posteriorly stomach sounds and intestinal gurgling were somewhat pronounced.

Neither the liver nor the spleen were palpable; no free fluid was demonstrable in the abdomen and there was no edema of the lower extremities.

Blood Pressure Reactions.—Oscillations were obtained by the Pachon method from the brachial artery as high as 138 and as low as 40 mm.

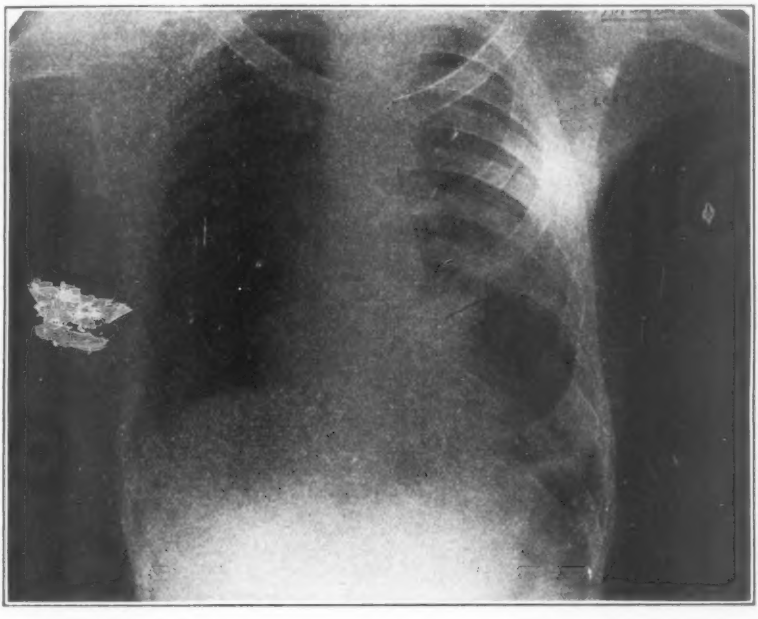


Fig. 2.—Roentgenogram of chest showing displacement of the mediastinum toward the right with the left diaphragm held high.

of mercury. The curve described was rather normal. Clinical blood pressure levels were established as systolic 108 and diastolic 65.

Vital Capacity Estimations.—The total volume of expired tidal air was 2200 c.c. Based upon the patient's weight of 148 pounds this represents a reduction to 50 per cent and based upon his height of 67½ inches this is a reduction to 52 per cent of his theoretical normal standard (Myers Tables).[5]

Fluoroscopic Examination showed the entire mediastinum displaced into the right chest, deforming the normal contour of the heart. The movements and pulsations of the ventricles and the great vessels were normal. The left diaphragm was fixed high in the chest at the level of the fifth rib anteriorly; it did not move with respiration and

the gas bubble of the stomach was seen above the level of the apex of the heart. The right diaphragm showed good respiratory excursions.

Orthodiagraphic Measurements were disturbed by the displacement of the mediastinum, but the heart did not appear enlarged.

A roentgenogram of the chest showed essentially the same findings; the left diaphragm was seen held high in the chest apparently by the gas bubble of the stomach. Many adhesions bound the left diaphragm to the chest wall and pericardium. (Fig. 2.)

The lower left lobe of the lung was clouded by what appeared to be a thickening of the pleura in this region; there was an associated increase in the peribronchial shadows.

Direct electrocardiographic studies were attempted after the method of Rothberger of Vienna; it has been the privilege of one of us (A. S. H.) to assist in the taking of direct tracings upon the operating table at the Allgemeine Krankenhaus in Vienna in a patient who was being operated upon for malignant disease of the lung. Special needle

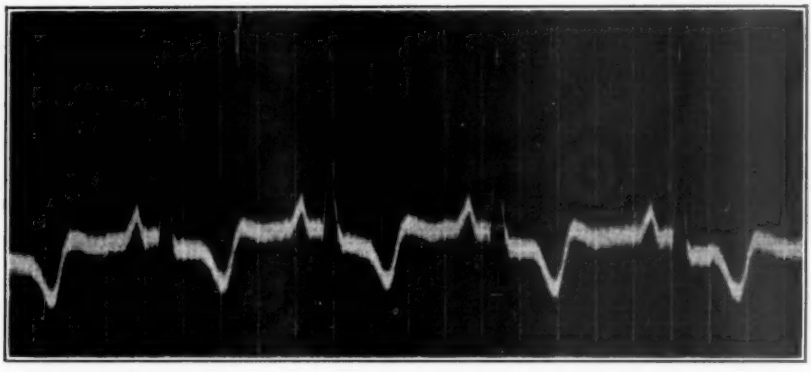


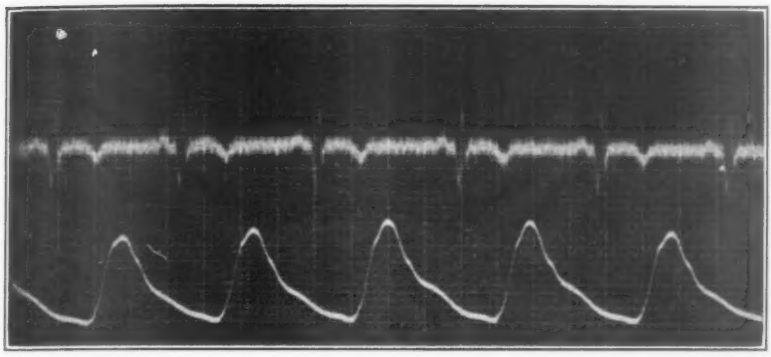
Fig. 3.—Direct electrocardiographic tracing, Lead I, taken March 16, 1926.

electrodes* were obtained and used in order to secure maximum string excursions. Unfortunately, however, the needles had only been applied in the first position corresponding to Lead I when the patient fainted, apparently unnerved by the manipulation of the recording apparatus. Enough of Lead I was secured for adequate examination before the experiment was thus precipitously stopped. (Fig. 3.)

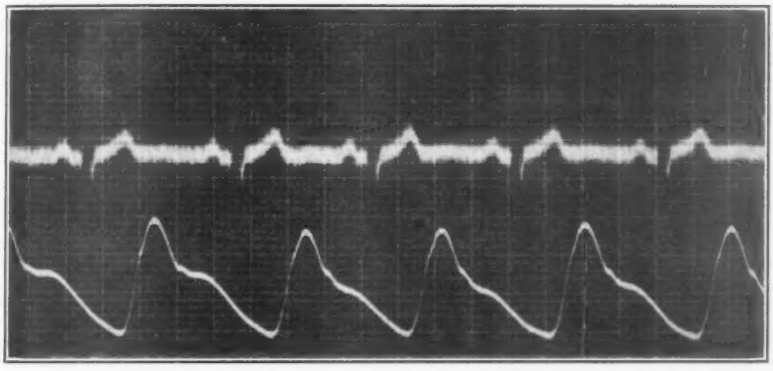
Analysis of this tracing shows upright and well formed P-waves and a constant P-R interval measuring 0.18 seconds. The QRS complex is upright and of considerable amplitude (2.7 cm. with 1.0 cm. equalling 1 millivolt standardization); its conduction time is within normal limits measuring about 0.12 seconds.[6]

The T-waves are inverted and vigorous; the first limb is "bowed" after the type described by Oppenheimer, while the second tends to

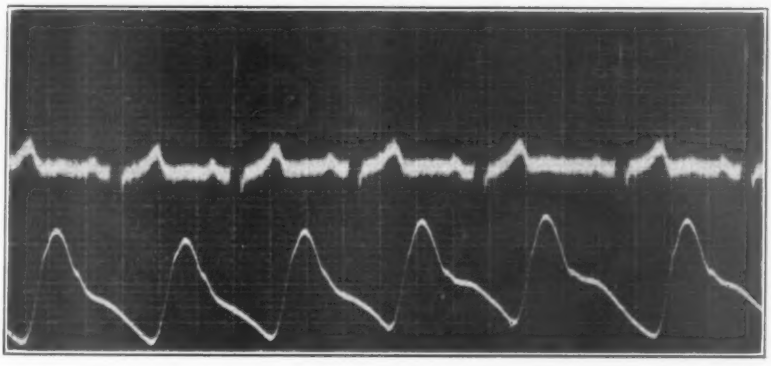
*These needle electrodes originally devised by Rothberger were modified for use at the Herzstation of the Verein Poliklinik in Vienna by Dressler, a set of which were brought back to New York by one of us (A. S. H.).



Lead I.



Lead II.



Lead III.

Fig. 4.—Second electrocardiographic and polygraphic study made on April 6, 1926, nine months after accident.

be somewhat diphasic as it rises above the isoelectric line. The auriculoventricular rate is 68 beats per minute which is slower than the patient's usual pulse, as this tracing was taken immediately prior to the syncopal attack. A slight sinus arrhythmia is also noted.

Considerable persuasion was necessary before the patient would again agree to submit to subsequent examination, and indeed, several "rehearsals" were required before the patient could be made to remain quiet long enough to secure suitable electrocardiographic and polygraphic records. On April 6, about nine months after receiving the injury a second instrumental study was made. (Fig. 4.)

Simultaneous brachial artery polygraphic tracings were taken with each of the three leads; the electrocardiographic records were taken in the usual manner from both wrists and the left leg as the patient would not permit the use of the needle electrodes to the percordium.

Lead I still showed inversion of the T-waves, perhaps somewhat less marked than before. The T-waves were no longer, however, of the "Oppenheimer type" as both limbs of the wave were symmetrical. There was little other change from the previous record except that the QRS complex has not the large amplitude obtained by the direct method. The auriculoventricular rate was now 84 beats per minute with an increased sinus arrhythmia.

Leads II and III were essentially normal. All waves were upright and well formed. The arterial pulse is well recorded and shows the time relation between the terminal ventricular complex and the propagated fluid wave from the left ventricle.

A third electrocardiographic study was made on July 7 about one year after the accident. (Fig. 5.) The patient's general physical condition had remained about the same and he had no specific complaints. He was employed in a garage and was able to do extremely heavy work without difficulty. His vital capacity had increased to 3600 c.c., representing a reduction of only to 86 per cent of his theoretical standard; Myers[5] believes that a reduction of 15 per cent is still well within a normal figure.

Analysis of these tracings shows a residual T-wave inversion in the first lead which has a tendency to become diphasic and appear above the isoelectric line in the first portion of the first limb; all other waves have remained about the same. The auriculoventricular rate has fallen to about 64 with a marked increase in sinus arhythmia.

During the breath-holding test of Rehfisch the pulse became somewhat irregular and upon closer examination the irregularity was found to be due to well compensated extrasystoles which occurred at the rate of 1 to 3 per minute.

Simultaneous polygraphic and electrocardiographic records were made during the course of the Rehfisch experiment.

Analysis of the tracings (Fig. 6) show the extrasystoles arising probably from the right ventricle but at points of irritability which are not constant. In Lead I the premature beat occurred rather late in diastole and hence was productive of a nonexhaustive type of extrasystole since the ventricles had sufficiently filled to open the aor-

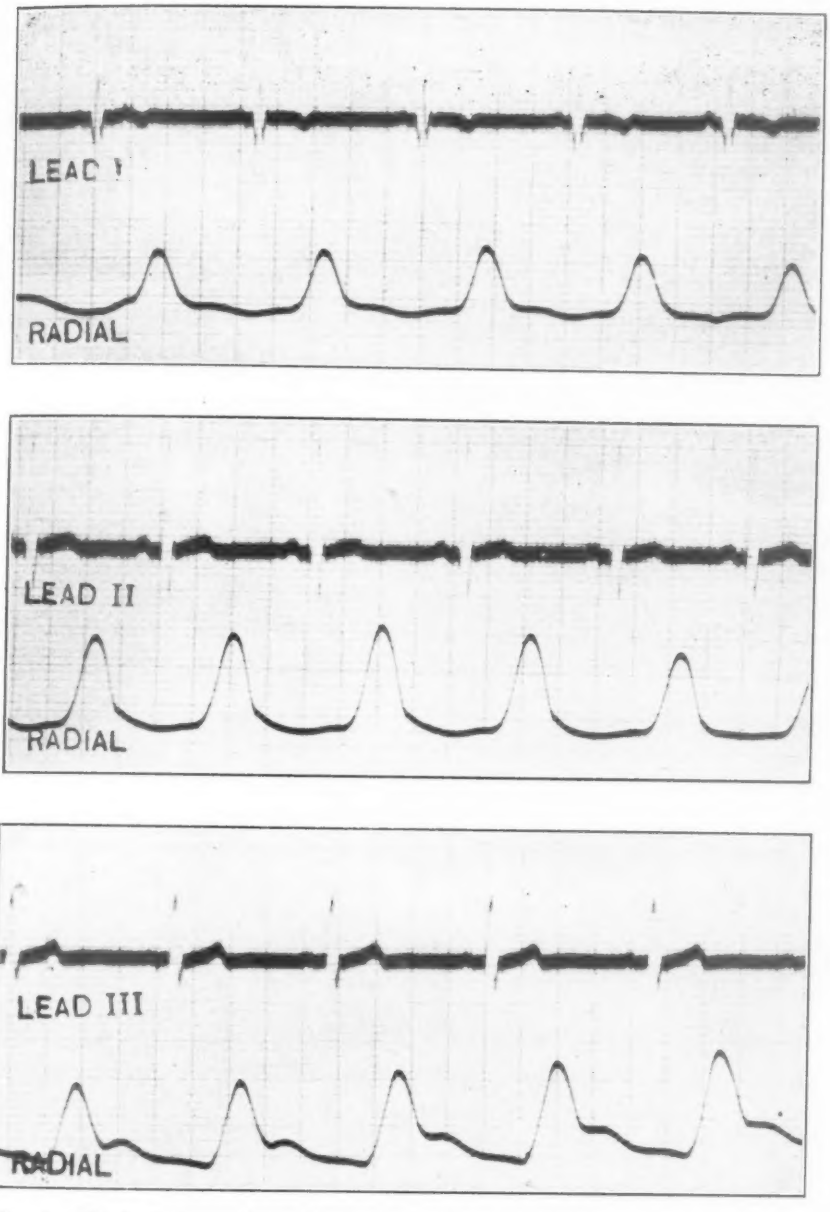


Fig. 5.—Third electrocardiographic study on July 7, 1926, about one year after accident.

tic valves. In Lead III the premature beat occurred rather early in diastole and it thus became ineffective; no corresponding beat is seen in the arterial pulse at this instant. It would thus appear that there was more than one new focus of stimulus production at play in the release of the premature beat.

COMMENT

Extensive and deeply penetrating wounds of the heart, usually considered if not promptly fatal as sufficient cause for rendering the myocardium insufficient, may be entirely recovered from. The literature records several such interesting cases: Cecchini[7] of Rome has followed two such cases for nearly twenty years. Both were deep stab wounds requiring suture. Long[8] has recently reported two similar cases. Hesse[9] followed twelve cases in Germany for several years;

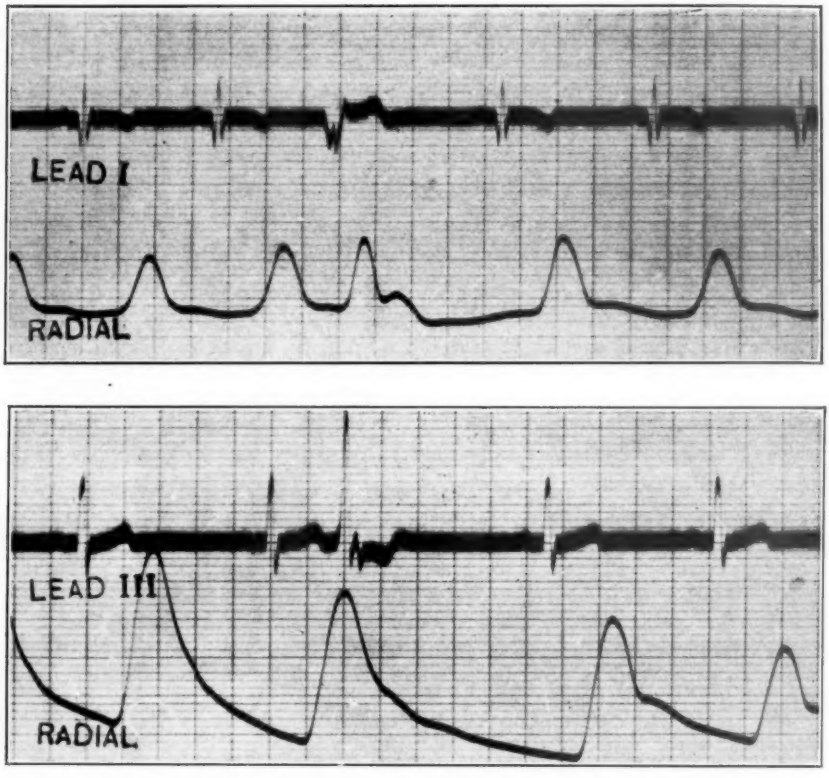


Fig. 6.—Simultaneous electrocardiographic and polygraphic studies made of extrasystoles occurring during the Rehfisch experiment.

in his experience conduction disturbances, if they do occur, quickly recover. Rojas and Elizolde[10] record three cases occurring in South America which they have watched. Davenport's case, however, is the most complete; quoting Smith[11] he noted that T-wave inversion occurred in all three leads similar to that produced experimentally by ligation of the coronary arteries in a dog. The T-wave inversion in Davenport's case persisted for about eight months and then all waves became upright. No extrasystoles or irregularities of the pulse were noted.

In the case herewith reported the T-waves became inverted only in the first lead and while the inversion has become less marked, yet it is still present one year after the accident. The development of the extrasystoles is also of extreme interest, more especially as they are apparently arising in the myocardium of the right ventricle, whereas the original injury and the buried foreign bodies are within the left ventricular wall. There is considerable opportunity for academic speculation as to the reason for this; the original experimental work of Winterberg and Rothberger in demonstrating the development of extrasystoles from irritating foreign bodies buried in the myocardium of laboratory animals would not seem to explain the matter.

The rather unexpected experience obtained by manipulation of the patient's heart through the rib-denuded area is also difficult to explain; squeezing of the apex produced a sharp, agonizing pain referred to the left shoulder. There was apparently no retrosternal pain or sensation and no referred pain to the left arm and hand, yet one could not but draw a mental comparison between the apprehensive attitude of this patient and one undergoing an anginal attack.

A further by-effect in this case is the paralysis of the left diaphragm which occurred after the accident and which suggests that the left phrenic nerve was severed in the original stab wound or at the time of the operation. The gradual development of the diaphragmatic hernia has caused the entire mediastinum to be displaced into the right chest and is somewhat complicating the pure cardiac syndrome.

The subsequent observation of this case should offer much material for the consideration of the cardiopathies, especially in regard to the fate of foreign bodies in the myocardium and in the restoration of a disturbed coronary circulation in an otherwise normal heart.

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Department of Reviews and Abstracts

Collective Review

AURICULAR FIBRILLATION*

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INTRODUCTION

THE contributions to our knowledge of auricular fibrillation have been many, and have extended over a considerable period of time. They include much accurate observation and brilliant experimental work, and some speculation. In this review the attempt is made to present only the more important phases of the subject; it is realized that the references are by no means complete.

That the heartbeat could be completely irregular had long been known, but it was only after it had been studied by means of the polygraph that this type of arrhythmia was recognized as a clinical entity. Further observations, made with the string galvanometer, established the fact that complete irregularity of the heart is due to fibrillation of the auricles. The nature of auricular fibrillation was then investigated, and by the use of the string galvanometer it has been demonstrated that the fundamental mechanism of this disorder is a circus rhythm in the auricles. Finally, the effects of the drugs commonly used in the treatment of auricular fibrillation have been studied by means of the string galvanometer, and the manner in which they act has been elucidated. A review of auricular fibrillation illustrates in a striking manner the importance of exact observations and methods of precision in medical science.

The subject of auricular fibrillation has been reviewed recently by Rothberger,[1] de Boer,[2] Garrey,[3] and Lewis.[4] I am indebted to these writers for their collections of references. Attention is directed also to an interesting historical paper by Lewis[5] in 1912.

HISTORICAL

The arterial pulse of auricular fibrillation is grossly irregular. It has been recorded by Marey,[6] Sommerbrodt,[7] Riegel,[8] Hering,[9, 10, 11] and others. In 1899 Cushny[12] described the effect of experimental faradiza-

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tion of the auricles in animals, which was known to produce auricular fibrillation; it had been described briefly by McWilliam[13] in 1887. Cushny noted the complete irregularity of the arterial pulse, and pointed out its similarity to the completely irregular arterial pulse observed clinically. He suggested that the clinical condition is due to fibrillation of the auricles, and repeated this suggestion in a paper with Edmunds[14] in 1907.

The venous pulse of auricular fibrillation is characterized by the absence of the "a" wave of auricular systole and the presence of one large wave due to ventricular systole. It has been named the ventricular type of venous pulse. The prominent systolic pulsations in the veins of the neck were described by Skoda[15] in 1850 and by Bamberger[16] in 1857. It remained, however, for Mackenzie[17] to point out, in 1902, that the ventricular form of venous pulse is associated with complete irregularity of the arterial pulse. He attributed both phenomena to a common cause,—paralysis of the auricles. Although this explanation was later abandoned, he established the fact that the disorder is a clinical entity. In 1904 he[18] still adhered to the theory of paralysis of the auricles, but differentiated a small group of cases in which he thought the auricles and ventricles contracted simultaneously. He was led to propose the theory of paralysis of the auricles because all signs of normal auricular activity were absent, and because postmortem the auricles were found to be dilated and thin-walled. Subsequently he observed cases in which the auricles were found to be hypertrophied, and others which reverted to normal rhythm. He accordingly abandoned the idea of paralysis of the auricles, and in 1907[19, 20] attributed the condition to simultaneous contraction of the auricles and ventricles, with the impulse arising in the junctional tissues. In these papers he pointed out the presence in the longer diastoles of the venous pulse tracings of some of the cases of small waves which he attributed to fibrillation of the auricles. He also called attention to the disappearance of the presystolic murmur in mitral stenosis with the inception of the complete irregularity; this murmur was replaced by a diastolic murmur. He abandoned the theory of "nodal rhythm" when true cases of nodal rhythm were demonstrated.

The small auricular waves occurring in diastole were described in 1907 by Wenckebach[21] and in 1908 by Hering.[10, 11] Hering noted the association of the completely irregular arterial pulse and the ventricular form of venous pulse, and attributed the latter to tricuspid insufficiency. The small auricular waves in the venous pulse have been recorded by Lewis,[22] Jolly and Ritchie,[23] Rihl,[24] Wiggers,[25] Niles and Wiggers,[26] and others. Lewis, Jolly and Ritchie, and Rihl attributed them to auricular fibrillation, but Wiggers and Niles attributed them to other mechanical phenomena because they did not correspond to the intraauricular pressure curves.

Auricular fibrillation was first recorded electrocardiographically by Einthoven[27] in 1906. Since then it has been studied by Lewis,[28, 22] Rothberger and Winterberg,[29] Jolly and Ritchie,[23] and many others. These observers pointed out that the electrocardiograms of auricular fibrillation are characterized by the absence of normal auricular P-waves, the presence of small auricular oscillations, complete irregularity of the ventricles, and ventricular complexes of the supraventricular type. The small auricular oscillations were attributed to fibrillation of the auricles and were shown to be independent of somatic tremor. Drury and Iliescu[30] subsequently demonstrated that, although they varied considerably from one instant to another, the presence and amplitude of such oscillations were independent of respiration. Jolly and Ritchie estimated the rate of the auricular oscillations to be 390 to 522 per minute in human beings, while Drury and Iliescu found it to vary between 300 and 600, with an average of 473.

Jolly and Ritchie[23] in 1910 described auricular flutter as an entity distinct from fibrillation. A little later Lewis[31] demonstrated that flutter may pass into fibrillation and that digitalis may cause the transition, and considered flutter to be closely related to fibrillation. In 1913 Ritchie[32] recorded the transition from flutter into fibrillation.

Lewis[28, 22, 5] and Rothberger and Winterberg[29] independently and almost simultaneously presented evidence which demonstrated conclusively that complete irregularity of the heart is due to fibrillation of the auricles. Lewis[22] based his conclusions on clinical and experimental observations which were in close agreement; in the experiments fibrillation of the auricles was known to be present. In each the radial pulse was completely irregular, both in rhythm and force; the venous pulse was of the ventricular type, the "a" waves were absent, and rapid small undulations were present in the longer diastoles; electrocardiograms showed the ventricles to be irregular with complexes of the supraventricular type, the absence of P-waves, and the presence of continuous oscillations shown to be of auricular origin. Lewis[4, 22] has seen the auricles fibrillating in a horse which had a disease similar in many respects to clinical auricular fibrillation with cardiac failure. Cutler, Levine and Beck[33] have seen fibrillation in the human auricle, which was greatly dilated. They described the movement in the appendage as occasional "irregular convulsive contractions." In the light of all this evidence there now remains no reasonable doubt that complete irregularity of the heart is a clinical entity due to fibrillation of the auricles.

Prior to the demonstration of circus movement as the mechanism of auricular fibrillation it was generally believed that the mechanism was a rapid and irregular elaboration of impulses by one or several independent foci in the auricles. This view was originally expressed by Engelmann[34] in 1895 in discussing the mechanism of ventricular fibrilla-

tion. It was subsequently applied to auricular fibrillation by Winterberg,[35] Lewis,[31, 36] and Rothberger and Winterberg.[37] Lewis developed the idea in his theory of heterogenesis, while Rothberger and Winterberg gave it the name of tachysystole. In 1912-13 Lewis[31] pointed out that auricular extrasystoles, paroxysmal auricular tachycardia, auricular flutter and auricular fibrillation had certain features in common. He stated, "the conclusions that (1) Single premature auricular contractions, (2) small groups of the same, (3) paroxysms of tachycardia from single auricular foci, (4) auricular flutter, (5) paroxysms of tachycardia from two or more auricular foci, and (6) auricular fibrillation arise essentially in the same manner; namely, through the pathological or heterogenetic origin of new impulses in the auricle, are clearly suggested by the facts at our disposal." In 1914 Rothberger and Winterberg[37] attributed auricular fibrillation to a pronounced acceleration of the auricles to rates of 3000 to 3500 per minute, but Lewis[4, 38] believes that they failed to distinguish between fibrillation and the state of rapid reexcitation.

CIRCUS MOVEMENT

In tracing the development of our knowledge of circus movement Lewis[38] emphasized our indebtedness to several independent workers. In 1876 Romanes[39] showed that the umbrella of the jellyfish is excitable and that it conducts impulses when stimulated. In 1887 McWilliam[13] in discussing fibrillation of the ventricles suggested, apart from the possibility of rapid spontaneous discharges of energy by the muscle fibers, another probable cause of the continued and rapid movement; namely, that the contraction might be propagated through the anastomosing muscle cells from one contracting fiber to another over which the contraction wave had already passed. The possibility that a single excitation wave may pass more than once through the same tissue, and that two or more beats may result from the same impulse was thus recognized by McWilliam. This possibility has also been recognized by Wenckebach[40] and others. In 1908 Mayer[41] reported the observation that a single contraction wave can be made to pass in one direction continuously around a ring cut from the disc of a jellyfish. Mines[42] in 1913 confirmed and extended Mayer's observations, and demonstrated circus contractions in rings cut from the auricles of ray fish. He suggested that circus rhythm was the underlying mechanism of delirium cordis or fibrillar contraction.

According to Lewis[38] "we are not indebted to Mines for the proof of circus movement, but to Mayer; we are not indebted to him for the first suggestion that fibrillation has circus movement underlying it, but to McWilliam. Our debt to Mines is that his observations into the factors underlying circus movement were thorough and illuminating, that when he resuggested circus movement as the underlying cause of fibrillation, the suggestion was so reinforced that its most careful consideration be-

came inevitable; it became the more inevitable when Garrey[43] in 1914 independently made the same suggestion and showed that in a ring cut from a fibrillating ventricle a single wave continues to circulate."

The final proof that circus movement is the underlying mechanism of auricular flutter and fibrillation appeared in 1920 and 1921 as the result of the brilliant investigations of Lewis and his collaborators, Feil, Stroud, Cotton, Drury, Bulger, and Iliescu.[44, 45, 46, 47, 48, 49, 50, 51, 38, 52, 53] Their experiments may be summarized as follows:

Auricular flutter and fibrillation were observed in dogs as an after-effect of faradic or rapid rhythmic stimulation of the auricles. By recording the auricular activity electrocardiographically from direct leads, they were able to time accurately the arrival of the excitation process at many different points in the auricular walls, and to determine its direction. In this manner it was possible to trace the course pursued by the excitation process. It was found that in both fibrillation and flutter a single impulse traveled continuously in a circular path in the auricles, and further that in flutter, which is extremely uniform, each revolution of this impulse corresponded exactly in its duration with the auricular cycles recorded simultaneously in the axial limb lead. Finally, when patients with fibrillation and flutter were studied by means of chest leads (in which the auricular oscillations are larger and more distinct than in the standard limb leads) taken in three planes, and the electrical axis of the auricles determined for each fiftieth of a second, it was shown that this axis revolves during the progress of each auricular cycle through 360 degrees. It was found that in flutter the circular path is remarkably uniform, while in fibrillation it varies somewhat. The path is usually around the natural ring of muscle which encircles the orifice of one or both great veins in the right auricle. The conclusion that in auricular flutter and fibrillation a single wave travels continuously in a circular path and that from this central circus movement impulses are given off to the outlying parts of the auricular wall is justified and has received wide acceptance.

Many of the factors involved in circus movement were studied in great detail, particularly conduction, the refractory period, and the action of the vagus nerves. They emphasized the influence of the refractory period upon conduction, introduced the conception of the partially refractory state and showed that it accounted for the irregular conduction and the deviation of the impulse from a uniform path in auricular fibrillation. It was found that stimulation of the vagus nerve shortens the refractory period and, in the presence of circus movement, increases the rate of conduction and the number of auricular cycles per minute.

Circus movement in the auricles is described as a wave traveling in a circular path; the crest of the wave advances into responsive

muscle, but it is followed by a wake of refractory muscle. Between the retreating wake of refractory muscle and the crest of the advancing wave is a gap of responsive muscle. The presence of this gap of responsive muscle in a circle of refractory muscle is essential for the maintenance of the circus movement. If the gap of responsive muscle should be abolished the crest of the advancing wave would meet refractory tissue which could not receive it. The circus movement would then cease, unless a longer path were open to it. The extent of the gap depends upon three factors: the length of the path, the rate of conduction, and the duration of the refractory period. The gap is increased if the path becomes longer, if conduction becomes slower, or if the refractory period becomes shorter; it is decreased or abolished if the path becomes shorter, if conduction becomes more rapid, or if the refractory period becomes longer. These factors are in themselves closely interdependent.

Lewis, Drury, Iliescu, and Wedd[54, 55, 56] investigated the effects of atropine, strophanthin, and quinidine in auricular fibrillation and flutter and found them, as well as those of vagal action, to be in complete harmony with the theory of circus movement. Atropine, of course, has an effect opposite to that of the vagus; it acts by removing the normal vagal tone. It increases the refractory period, slows conduction, and decreases the number of auricular cycles per minute. The effects of the vagus and of atropine in circus movement of the auricles will appear paradoxical unless the great difference between this mechanism and the normal auricular mechanism is kept clearly in mind.

Strophanthin was found to shorten the refractory period and to increase the rate of conduction and the number of auricular cycles per minute. These effects result from stimulation of the vagus centers by the drug, and almost invariably occur. The direct effects of the drug upon the auricular muscle are quite the opposite but they are rarely apparent because the vagus effects nearly always predominate. A decrease in the refractory period may open a shorter path to the circulating wave and in this manner convert flutter into fibrillation.

Quinidine was shown to lengthen the refractory period and to decrease the rate of conduction and the number of auricular cycles per minute. These effects result from the direct action of the drug upon the auricular muscle; they are enhanced somewhat by the reduction of vagal tone produced by the drug. An increase in the refractory period tends to close the gap of responsive muscle. If the gap is abolished the circulating wave must follow a longer path; in this manner fibrillation is converted into flutter. If the gap is abolished and a longer path is not open to the wave, the circus movement ceases and normal rhythm is restored. On the other hand, retarded

conduction increases the gap, and when this effect predominates the auricles may be greatly slowed but the circus movement persists.

Regarding the effects of these drugs when used in combination, it has been found that digitalis does not diminish the quinidine effect appreciably in practice, and that it may be of value in preventing or controlling the rapid ventricular beating which often occurs during quinidine administration. Atropine, although it may abolish fibrillation in dogs, does not appear to be of any practical value in increasing the effects of quinidine.

Attention is directed to the fact that when the refractory period is increased conduction is slowed, and when the former is shortened the latter improved. The relation between the two is obvious. Actually, according to Lewis, Drury and Iliescu,[57] the speed of conduction in any single auricular muscle fiber is uniform; if it conducts, it conducts at normal speed.* The apparent variations in conduction rate are attributed by them to deflection of the wave from the shortest path by small local blocks of refractory tissue. The term, "rate of conduction," has been used in the foregoing discussion in the convenient and broad sense.

THE EFFECT OF AURICULAR FIBRILLATION UPON THE VENTRICLES

According to Mackenzie's earlier views of complete irregularity of the heart the ventricular beat arose independently of the paralyzed auricles,[17] or in the auriculoventricular node.[19] In 1904-5 Fredericq[58] showed that in experimental auricular fibrillation impulses from the auricles traverse the auriculoventricular bundle. Hering[11] in 1908 presented evidence of the supraventricular origin of the ventricular beats. In the next year, when it was shown that complete irregularity of the heart is due to fibrillation of the auricles,[22, 28, 29] it was further demonstrated that the ventricles responded to stimuli from the auricles. The auricular impulses are showered upon the ventricles rapidly;[22] they are irregular and are conducted to the ventricles irregularly. Not all of them reach the ventricles; the refractory period of the auriculoventricular node is about 30 per cent longer than that of auricular muscle.[54] The node is a natural blocking point, and many of the auricular impulses are blocked by it; it prevents extreme ventricular rates in response to the auricles. The ventricular contractions are, however, usually quite rapid, 110 to 150, and it is then that their irregularity, the absence of a definite relationship between the force of the beat and the length of the preceding diastole, and the discrepancy between the ventricular and the radial pulse rates become most pronounced.[22] In 1910-11 Mackenzie[59] pointed out the inaccuracy of blood pressure estimations by the usual methods when the pulse was continuously irregular. James and Hart[60] in 1914 em-

*Lewis, Drury, Iliescu and Wedd[55] have suggested that quinidin may retard conduction independently of its effect upon the refractory period.

phasized this inaccuracy and proposed a more accurate method of determining the "average systolic blood pressure" in auricular fibrillation.

It was suggested by Lewis[22] in 1909-10 that in auricular fibrillation the ventricles are working at a disadvantage and that "the energy developed and used up is great in proportion to the work accomplished." James and Hart pointed out that many of the ventricular beats are too weak to open the aortic valves; they also stressed the discrepancy between apex and radial pulse rates and adopted the term, "pulse deficit," proposed by Robinson and Draper. In 1915 Wiggers,[25] who studied the intraventricular pressure, and in 1920 Eyster and Swarthout,[61] pointed out that some ventricular beats are too feeble to open the semilunar valves. Gesell[62] in 1916 presented evidence that the ventricular volume output is less in auricular fibrillation than in normal rhythm, although it is greater than that maintained by venous pressure alone.

From the foregoing it appears obvious that the ventricles are working at a great disadvantage in auricular fibrillation. This disadvantage is further emphasized by the statements of Mackenzie,[63, 64, 65] Lewis,[66] Wilson,[67] and others that cardiac failure in patients may result from the onset of auricular fibrillation. Lewis[66] attributes the cardiac failure in large part to the acceleration of the ventricles. Further evidence regarding the effect of auricular fibrillation upon the circulation is obtained from a study of those patients in whom normal rhythm has been restored by quinidin, which will be discussed later.

In auricular fibrillation the ventricles may be slowed by stimulation of the vagus nerve[68, 69, 70, 71, 72] and by digitalis.[22, 59, 63, 64] Digitalis may produce complete heart-block,[73, 74, 75] in which case the ventricles are slow and regular. Complete heart-block may, however, occur in auricular fibrillation independently of digitalis ([22, 58, 76, 77, 78] and others), and here, too, the ventricular beats are slow (30 to 40) and regular. Stokes-Adams attacks may occur in the presence of auricular fibrillation.[22, 77, 79] Ventricular extrasystoles occurring during auricular fibrillation are frequently encountered in clinical electrocardiograms. They are most readily recognized clinically when they produce coupling; in this condition the uniformity of the cycles immediately preceding the extrasystoles makes it clear that they are of ventricular and not auricular origin.[22, 80] Gold and Otto[81] observed digitalis bigeminy six times as often in patients with auricular fibrillation as in those with a regular sinus rhythm.

THE ACTION OF THE VAGUS NERVES

Lewis[22] in 1909-10 observed the effect of stimulation of the vagus upon the fibrillating auricles of dogs. The muscular activity became more finely subdivided and more flickering (see also references[68, 69]).

In 1911 Robinson and Draper[71] studied the effect of mechanical stimulation of the vagus nerve in patients with auricular fibrillation, and observed slowing of the ventricles, but the electrocardiograms revealed no appreciable effect upon the fibrillating auricles. Rothberger and Winterberg[37] in 1914 reported that stimulation of the vagus makes the auricular oscillations in the electrocardiogram smaller and more rapid, and stated that it shortens the refractory period. In 1921 Lewis, Drury and Bulger[50] presented evidence that stimulation of the vagus increases the rate of the fibrillating auricles, the result of shortening the refractory period and improving conduction.[49] They also observed that stimulation of the vagus may convert auricular fibrillation into the state of rapid reexcitation. This was studied more fully by Lewis, Drury and Iliescu.[57] In 1924 Blumgart[82] pointed out that in auricular fibrillation in man when exercise increases the ventricular rate it usually lowers the auricular rate; this is ascribed to diminished vagal tone. In some instances in animals stimulation of the vagus may result in the cessation of auricular fibrillation and the return of normal rhythm.[22, 50]

It has been mentioned that stimulation of the vagus slows the ventricles in the presence of auricular fibrillation. This was observed in dogs in 1904-05 by Kronecker and Spallitta[68] and Phillips,[69] and since then by others.[22, 83, 84] This is ascribed to depression of auriculoventricular conduction, as was suggested by Cushny and Edmunds[14] in 1907. Robinson[83] found that the right and left vagi were equally effective in blocking impulses from the fibrillating auricles of dogs. Wenckebach[70] and Robinson and Draper[71] and others have observed slowing of the ventricles upon stimulation of the vagus in patients with auricular fibrillation.

ETIOLOGY

That auricular fibrillation is extremely common is shown by the observation of Lewis[22] that of 114 cases with persistent irregularity of the heart 50 per cent had this disorder. In a series of 1500 consecutive patients with cardiac symptoms and signs studied by White,[85] 198, or 13 per cent, had auricular fibrillation, and of these 170, or 86 per cent, had demonstrable evidence of "organic" heart disease. Attention has been called by Mackenzie,[65] Lewis,[22, 28] Lea,[86] Levine,[87] Cowan and Ritchie,[88] and others to the frequent association of mitral stenosis and auricular fibrillation. That the disorder is often due to degenerative myocardial changes has been pointed out by Lewis,[28] Mackenzie,[65] Lea,[86] Cowan and Ritchie,[88] and others. The frequent occurrence of auricular fibrillation in goiter has not been sufficiently emphasized; Krumbhaar,[89] Kerr and Hensel,[90] Wilson,[67, 91] Baumgartner, Webb and Schoonmaker,[92] Foster,[93] and others have referred to it. From a study of 15 patients with goiter and auricular fibrillation,

Dunhill, Fraser and Stott[93a] concluded that partial thyroidectomy removes the cause of the fibrillation, and that following this operation normal rhythm often returns spontaneously or it is readily restored by quinidine. Toxic goiter is extremely common in this clinic; auricular fibrillation has been recorded electrocardiographically in 15 per cent of these patients, and it occurs as a transient disturbance in many more.[94] Levine and Cowan and Ritchie have pointed out that auricular fibrillation is rare in syphilitic heart disease; the latter authors stated that it is rare in aortic regurgitation also (see reference [22]). The accompanying table shows the percentages of auricular fibrillation found to have mitral stenosis, syphilis, etc.

	HISTORY OF RHEUMATIC INFECTION	MITRAL STENOSIS	DEGENERATIVE CHANGES	SYPHILIS
Lewis	64.4	20.8	Common	
Lea	56.6	31.3	32.8	
Levine	76.4	35.5		8.6
Cowan and Ritchie	35.7	Common	Common	14.7

Lewis, Drury and Bulger[49] state that circus movement is provoked in the auricle when an effective stimulus enters its muscle while it is in the partially refractory state. Auricular extrasystoles have been observed frequently during the intervals of normal rhythm in patients with paroxysmal auricular fibrillation,[95] and prior to the onset of auricular fibrillation in others.[22] In this clinic, however, they have been recorded in only 2.5 per cent of patients with toxic goiter.[94] Lewis[22] believes that a purely mechanical doctrine of the cause of auricular fibrillation, such as distension of the auricles, is not tenable, and that the cause of fibrillation as it occurs clinically must be sought in the morbid anatomy of the auricular muscle. Wilson[67] considers that persistent auricular fibrillation is invariably associated with chronic changes in the heart muscle, although they may not at times be readily demonstrable by our present anatomical methods.

MORBID ANATOMY

As attention was drawn successively to "Wenckebach's bundle," the auriculoventricular node, and the sinoauricular node, investigators sought in the morbid anatomy of these structures the explanations of various disorders of the heartbeat. The lesions which were found did not always have the meanings at first attributed to them. Nevertheless these observations demonstrated that anatomical changes are frequently present in the auricular muscle of patients with auricular fibrillation. Müller[96] in 1905, and Wenckebach[21] in 1907, reported lesions of the auricular muscle. Schönberg[97, 98] in 1909 described areas of lymphocytic infiltration and of fibrosis in the auricular muscle of cases of auricular fibrillation, but found similar lesions in cases

without fibrillation. In 1910 Hedinger[99] found lymphocytic infiltration and granulation tissue in the auricular walls in cases of fibrillation, and Koch[100] described sclerotic changes in the sinoauricular node. Mackenzie[101] stated in 1913 that while no lesion is constantly associated with auricular fibrillation, and the specialized tissue is not necessarily affected, yet anatomical changes, myocardial degeneration, cellular infiltration, or anemic infarction due to coronary disease are often found. In 1914 Jarish[102] reviewed the literature and reported the frequent occurrence of fibrous changes or cellular infiltration in the auricular wall in cases of auricular fibrillation, and Lenoble[103] in 1921 described fibrosis of the auricular muscle. In a recent study of a large series of cases Frothingham[104] was unable to establish any relationship between anatomical changes in the auricles and the presence of auricular fibrillation. Cowan and Ritchie[88] have summarized the subject as follows: "Our own histological observations and those of others indicate that the auricular muscle is usually affected by a diffuse or patchy fibrosis, with or without cellular infiltration and other signs of subacute or chronic myocarditis. The essential lesions must be sought for in the auricular walls rather than in the primitive tissue, because the sinus node is not necessarily involved in the inflammatory process, whereas it may be inflamed although the auricular contractions are coordinate and rhythmic."

There remains a group of cases of auricular fibrillation in which no demonstrable anatomical changes are found in the auricular muscle. Is the explanation for the fibrillation in these cases to be found in other structures? Probably not. One is reminded of the occasional patient with abundant clinical evidence of myocardial disease, who may even die of myocardial failure, in whom the pathologist finds no abnormality of the heart muscle (see reference [78]). The answer is to be found in the pathological physiology of the tissue cells, in physicochemical changes that defy detection by our present anatomical methods. In 1910 Lewis[22] suggested that local anemia of the auricular muscle might be a factor in the production of auricular fibrillation, and he and Mathison[105] showed that in cats asphyxia slows the sinus rhythm and depresses auriculoventricular conduction. Wilson[67] in 1923 stated that persistent auricular fibrillation is invariably associated with changes in the heart muscle, which may, however, be physicochemical in nature and impossible of demonstration postmortem. The studies of Carter, Andrus and Dieuaide[106] are of importance in this connection. They found that anoxemia in contractile tissue increases the hydrogen-ion concentration, and that an increase in the hydrogen-ion concentration increases the refractory period and depresses conduction. This may lead to the appearance of ectopic rhythms; reentrant waves and circus movements may be accounted for by regional or diffuse accumulations of hydrogen ions. Resnik[107]

reported in 1925 that when vagal tone is removed and the auricles are stimulated by a faradic current, the early effect of anoxemia is to predispose the auricles to fibrillation; the late effect is to inhibit the development of fibrillation.

DIAGNOSIS AND PROGNOSIS

Little could be added to the accounts by Mackenzie[17, 65] of the clinical features of auricular fibrillation. We are, however, especially indebted to Lewis for his clear description of the diagnostic features of this arrhythmia in his excellent monograph, "The Clinical Disorders of the Heart Beat." The complete irregularity of the heart is of prime importance in the recognition of the condition. If in addition the heart rate, as determined by auscultation at the apex, is over 120 per minute the disturbance is almost surely due to auricular fibrillation. If the heart is irregular but slow, an attempt may be made to increase its rate to 120 or more by means of exercise or drugs; if the irregularity persists and becomes more pronounced the condition is auricular fibrillation. The ventricular rate is usually high in untreated cases. Pulse tracings and electrocardiograms, of course, give conclusive evidence of auricular fibrillation.

The prognosis in persistent auricular fibrillation is usually not very good; in general the onset of fibrillation is the beginning of the end.[88] The patient may live for a few years in comparative comfort, but more than this is exceptional. Mackenzie[18, 63, 64, 65] has pointed out that the onset of auricular fibrillation is usually accompanied by signs of heart failure, and also that in the great majority of cases with heart failure and dropsy the onset of heart failure is due to auricular fibrillation. He stated, too, that the prognosis depends upon the condition of the heart muscle and its power to maintain an efficient circulation, and in large part also upon the manner in which the patient responds to treatment.[65] He has followed a patient with auricular fibrillation for sixteen years, while Heitz[108] described a case in which the condition was probably present for thirty-two years. Cowan and Ritchie[88] described a patient, a physician, aged eighty-five years, who was known to have had auricular fibrillation for six years, and who thought his heart had been irregular for forty years. Lea[109] reported a case with long standing auricular fibrillation who was found on one occasion to have a resumption of normal auricular contraction.

It is important to remember that, although auricular fibrillation is usually permanent, it may be transient or paroxysmal. As a rule, however, the tendency to recurrence of the paroxysms becomes progressively greater, until finally the fibrillation becomes permanently established.[65, 110] The transient form of auricular fibrillation is rather common in toxic goiter, and may disappear after thyroidectomy,[67, 89, 91]

and often appears as a temporary disturbance during or following surgical operations, especially during the stage of intoxication which often follows thyroidectomy. It occurs rarely in pneumonia and other acute infections.[111] The paroxysms may last for a few seconds or several days,[65, 95, 110, 112, 113] and auricular extrasystoles are often observed between the paroxysms.[95, 109]

TREATMENT

Rest, or a restriction of the patient's activities, and the measures indicated by the accompanying conditions, are usually very important. The greatest benefits, however, are often obtained only by the administration of digitalis or quinidine, of which the former is by far the more useful.

The effect of *digitalis* upon the fibrillating auricles has been mentioned previously. The auricular rate may be increased, decreased, or unchanged.[56] The first is the usual effect and is due to stimulation of the vagus by the drug, which results in a shortening of the refractory period.[50] The other effects are the result of the direct action of the drug upon the auricular muscle, causing a lengthening of the refractory period.[54] The effect of digitalis upon the fibrillating auricles, then, would tend to establish the disorder more firmly. Wilson,[67] however, has stated that "in very rare instances the auricles cease to fibrillate after and apparently as a result of digitalis medication. The opinion that this is a frequent occurrence is due to the fact that the arrhythmia may become inconspicuous when the ventricular rate is greatly reduced by the drug. The rhythm does not, however, become absolutely regular unless the treatment is pushed to the point of producing complete heart-block. In this connection it should be remembered that in complete heart-block produced by digitalis, bradycardia is not always present."[75, 87] When auricular fibrillation ceases during digitalis administration it may be due to the improved nutrition of the auricular muscle accompanying the general improvement in the circulation, or it may stop spontaneously in spite of, and not because of, the digitalis. Mackenzie[59] and others have seen digitalis induce fibrillation in patients with normal rhythm. Digitalis may convert flutter into fibrillation,[31, 114] and Ritchie[32] has succeeded in recording the transition. Wedd[115] also recorded the transition and observed a quickening of the auricles just before the change.

It has long been known that digitalis slows the ventricles in the presence of auricular fibrillation.[63, 64] This slowing is ascribed to the production by the drug of auriculoventricular block.[22, 28, 59, 116, 117, 118] The slowing has been attributed to stimulation of the vagus by the drug by Mackenzie[59] and Wenckebach,[70] while Cushny, Marris and Silberberg[118] and Cushny[119] ascribed the block to a direct effect of the drug upon the conducting tissue. Silberberg,[117] Lewis, Drury, Wedd,

and Iliescu[56] and recently Cushny[120] believe that the block is partly vagal and partly direct. Cushny[120] stated that the initial slowing is largely vagal, but after larger doses of digitalis the block must be chiefly direct. Digitalis may produce complete heart-block, as pointed out by Edens,[73] Taussig[74] and others. The ventricles are then regular and usually, but not always, quite slow.[4, 87] Dock and Levine[75] have pointed out that when digitalis produces complete heart-block the ventricular rate may be somewhat higher than is usually the case when the block is not of digitalis origin. They attribute this to an acceleration of the dissociated ventricle by digitalis, while Lewis[4] suggests that the digitalis block is located in the upper part of the auriculoventricular node and the ventricle responds to the lower part of the node which has a higher degree of rhythmicity than the ventricle itself. In the treatment of complete heart-block by full doses of digitalis the ventricular rate is often not increased.

Mackenzie[59] has observed that when fibrillation comes on in patients suffering from the degenerative changes of later life digitalis is often without effect on the heart's rate. It has been pointed out by many that in acute infections and toxic conditions digitalis sometimes does not produce the expected slowing, and Wilson[67, 91] has emphasized the failure of digitalis to affect the heart rate in the acute and severe thyroid intoxications, especially after operation. It should be pointed out, too, that as a toxic effect from large doses of digitalis there may be a ventricular tachycardia; this is readily demonstrated in the cat's heart. It has been reported in man by Danielopolu,[121] Schwensen[122] and others and has been especially studied by Luten.[123, 124] This advanced toxic rhythm may occur when the usual and earlier toxic effects have been absent, masked or overlooked, and when the ventricles are rapid and irregular in a patient who has received large doses of digitalis, this possibility should be kept in mind. The electrocardiogram reveals clearly the nature of the disturbance. The production of ventricular extrasystoles and coupling by digitalis has been mentioned.[18, 63, 64, 80, 81]

The great benefits resulting from the administration of digitalis to patients with auricular fibrillation have long been appreciated.[65, 88] Stewart and Scott[125] have demonstrated an increase in the rate of circulation after digitalis by measuring temperature changes in the hand. Lewis[66] attributed the cardiac failure in fibrillation largely to the very rapid, irregular, and ineffectual beating of the ventricles, and stated that the only beneficial action of digitalis is in slowing the ventricles in auricular fibrillation. Mackenzie[65] adopted a similar view. In addition to this very important effect of the drug, however, it has another action almost as beneficial; it increases the strength of the ventricular contractions. In 1910-11 Mackenzie[59] stated that "while there is no doubt that digitalis relieves distress of breathing and reduces dropsy, it does not necessarily do so by slowing the

pulse." Cushny[119] in 1917 attributed the improvement largely to the slowing of the ventricles, but stated that it may be due in part to the increase in the strength of the ventricular contractions, which could be demonstrated in animals experimentally. Christian[126] in 1919 and Luten[127] in 1924 demonstrated remarkable recovery from heart failure as a result of digitalis in patients with normal cardiac rhythm. Finally Cohn and Stewart[128] proved in 1924 that digitalis increases the amplitude of ventricular contraction in man; two of the four patients studied by them had auricular fibrillation, and they were able to show that the increased contraction was independent of the ventricular rate.

In auricular fibrillation, after the ventricles have been slowed, it is almost invariably necessary to keep them slow by continuing small doses of digitalis. Mackenzie[59] and others agree that the best results are obtained when the resting heart rate is kept below 70 and above 60 per minute. The amount of digitalis required to maintain this effect has been found by Whiting[129] to be about seven minims of the tincture three times daily. This dose represents the rate of disappearance of digitalis which Pardee[130] found to be equivalent to twenty-two minims of the standard tincture daily. These figures represent an average; the individual's requirement may vary somewhat from the average, but the exact dose necessary can readily be determined for each patient. Blumgart[82] has shown that the excessive and prolonged acceleration of the ventricles in response to exercise in patients with auricular fibrillation is not prevented by digitalis. For a complete discussion of digitalis the reader is referred to the monographs of Robinson[131] and Cushny.[120]

The introduction of *quinidine* has made it possible to restore normal rhythm in many patients suffering from auricular fibrillation and has thrown a new light on abnormal cardiac physiology. In 1914 Wenckebach[132] announced that auricular fibrillation could be abolished by quinine. Frey[133, 134] investigated various cinchona derivatives and reported in 1918 that quinidine, an isomer of quinine, was the most powerful in its action upon the fibrillating auricles. Since then this drug has been studied and used by many workers who have found that it restores normal rhythm in somewhat over half of the cases of auricular fibrillation.

The manner in which quinidine acts has been the subject of much fruitful research, and we are indebted to Lewis, Drury, Iliescu, and Wedd[55, 56, 135] for the most detailed account of its effects. They found that the drug slows the fibrillating auricles; it does this by lengthening the refractory period and depressing conduction. The former effect tends to abolish the gap of responsive muscle, which is necessary if the circus movement is to continue, and so terminates the fibrillation. The latter effect tends to increase the gap of responsive muscle and to preserve the fibrillation. When the former effect predominates fibrillation may be abolished; if the latter effect is the greater the

auricles may be greatly slowed, but the fibrillation persists. The action of the drug is twofold; it affects the heart muscle directly and also partially paralyzes the vagi, and both effects are in the same direction in regard to the alterations in the refractory period and conduction. The ventricular rate is usually conspicuously increased; this is an indirect effect due to the partial paralysis of the vagi and to the reduction of the auricular rate which permits more impulses to be transmitted through the junctional tissues to the ventricles. In its direct effect quinidine depresses auriculoventricular conduction, but this counteracts only partially the indirect effects. These workers showed also that atropine, though acting in the same direction, had little effect upon the action of quinidine on the fibrillating auricles, and was not of value in reinforcing the quinidine effect clinically. Digitalis was found to be of value in preventing the undesirable rise in ventricular rate accompanying quinidine administration, and to interfere very little with the effect of quinidine upon the auricles, although its action is in the opposite direction.

Hecht and Rothberger[136] observed that quinidine depresses conduction from auricles to ventricles, and Schott[137] stated that it may even produce block. Cohn and Levy[138] and de Boer[139] have demonstrated the lengthening of the refractory period and depression of conduction produced by quinidine. Drury, Horsfall and Munly[140] have reported a similar effect upon the dog's ventricle.

During quinidine administration certain abnormal ventricular complexes may be observed in electrocardiograms. They are characterized by an abnormally long QRS interval and resemble the complexes of ventricular extrasystoles or those of defective intraventricular conduction. Lewis, Drury, Wedd, and Iliescu[56] and Levy[141] consider that they are extrasystolic in origin and arise in the ventricles, while Korns[142] and Wilson, Wishart, Clark and Herrmann[143] attribute them to the defective conduction within the ventricles of impulses transmitted from the auricles. Most of the available evidence is in support of the latter view. Quinidine is known to increase the QRS interval[55, 136, 141, 142] and to depress conduction in the ventricles.[139, 140]

Lewis, Drury, Wedd and Iliescu[56] have studied the rapidity and duration of the effects of single test doses of quinidine, and the rate of elimination of the drug. The auricular rate begins to fall about a half hour after the oral administration of 0.6 to 0.8 gram of the drug. The fall of rate is completed usually in about two hours, the rate usually remains low for about one hour, and then rises gradually and reaches the original level in about twenty-four hours. The changes in ventricular rate correspond to those in the auricular, but are in the opposite direction. This, of course, has a direct bearing upon the frequency of the dosage in patients, and most workers give the drug in small doses and at frequent intervals, from four times daily to every two to four hours.[141, 144, 145, 146] Quinidine has been given by

vein to patients in doses of 0.2 to 0.4 gram by Boden and Neukirch[147] and by Wilson[148] who, however, does not advocate this method for the routine treatment of patients. Quinidine therapy is always to be preceded by an initial small dose of the drug to test for idiosyncrasy.

Not all of the effects of quinidine are beneficial. Many patients are not improved by the return of a normal rhythm and a few have died suddenly during quinidine administration. Many of the deaths can be attributed to embolism. Mackenzie[149] has pointed out that in the presence of auricular fibrillation, thrombi are likely to form in the auricular appendages and that by the restoration of normal auricular contraction such thrombi may be dislodged and carried into the circulation to produce embolism. He has pointed out, too, that embolism occurs spontaneously in auricular fibrillation and that it sometimes occurs when normal rhythm is restored by digitalis in auricular flutter. He emphasized the danger of embolism but did not believe that quinidine should be withheld when it was definitely indicated. Orr[150] has reported a case of paroxysmal flutter with frequent embolism associated with the resumption of normal rhythm. Ellis and Clark Kennedy,[151] Viko, Marvin and White,[152] Burwell and Dieuaide[145] and others have emphasized the danger of embolism. In reviewing the reported cases in which embolism occurred Burwell and Dieuaide found that eleven out of fourteen died as a result of this accident, but, as they pointed out, embolism occurs spontaneously in patients with fibrillation. Viko, Marvin and White consider embolism more likely to occur in fibrillation of long duration. Another danger from quinidine is the production of ventricular fibrillation, as in a case reported by Kerr and Bender,[153] which fortunately recovered. That temporary paralysis of respiration may result from quinidine is shown by the experiments of Gordon, Matton and Levine,[154] upon cats. They found that the animals could often be revived, even after the heart had stopped as a result of quinidine intoxication, by artificial respiration and caffein sodium benzoate. They rarely observed ventricular fibrillation even in profound intoxication. Because of the risks attendant upon quinidine administration, it is generally admitted that the drug should not be given to patients unless they are kept under close observation. The benefits obtained in some instances, however, amply justify the slight risk which is assumed.

In an analysis of 606 cases collected from the literature, Burwell and Dieuaide[145] found that quinidine restored normal rhythm in 339, or 55.9 per cent. Many cases, however, soon revert to auricular fibrillation. Most patients in whom normal rhythm persists are greatly improved, both subjectively and objectively.[144, 145, 152, 155, 156, 157] Ellis and Clark Kennedy[151] thought that the improvement in the patient's general condition was not striking, and Hart[155] believed that the improvement was no greater than that obtained by digitalis, but that normal rhythm was better than fibrillation because of the relief ob-

tained from the uncomfortable sensations produced by the fibrillating heart. Blumgart[82] found that the return of normal rhythm did not greatly alter the tolerance for exercise as shown by the response of the heart rate. Viko, Marvin and White,[152] Burwell and Dieuaide[145] and others, however, have reported striking improvement in those patients who remained normal. Stewart and Carter[156] and Stewart[157] studied the blood gases in cases of fibrillation and were able to demonstrate definite improvement in the circulation. They and others have observed an increase in the vital capacity after the return of normal rhythm. Stewart states that "these studies show that the circulation is improved by the restoration of the normal mechanism and offer a rational basis for the attempt to bring about reversion to the normal mechanism by the use of quinidine sulphate in selected cases. The advantages of quinidine therapy seem to be four: 1. Marked subjective improvement of the patient under normal mechanism, 2. Great increase in the cardiac reserve, 3. Improved pulmonary ventilation, 4. Improvement in the oxygen saturation of the venous blood, and on the basis of the coefficient of utilization, improvement in the peripheral systemic blood flow."

Regarding the selection of cases suitable for quinidine therapy there is pretty general agreement that fibrillation of short duration is more likely to respond favorably and to remain normal. Cases of long duration are more likely to revert to auricular fibrillation and to suffer from embolism. It is generally considered best to completely digitalize a patient before giving quinidine. After normal rhythm has been restored it is sometimes necessary to continue small doses of quinidine to prevent the return of fibrillation.

NOTE ON DECREMENT

The discovery by Drury and Andrus[158] in 1924 of a condition in heart muscle akin to decrement, as observed in a narcotized or cooled nerve,[159] has led to further important work on conduction and the refractory period in heart muscle. These workers perfused hearts with oxygen-free Ringer's solution, modified so as to make it slightly acid. They found that, if the fluid were sufficiently acid, a single impulse, as it traveled through the auricles, was conducted more and more slowly, and that the electrical deflection produced by it became smaller and smaller, until finally the impulse died out altogether. Drury[160] in 1925 observed this same phenomenon in auricular muscle injured by compression or by cooling. In the same year Lewis and Master[161] reported the same disturbance in conduction from auricles to ventricles in hearts in which partial block had been produced. Reexamination of the original curves of Lewis and his coworkers, in their studies of the refractory period and the effects upon it of drugs, showed that this condition was present in some of those experiments. Drury and Love[162] found that veratrin produces in auricular muscle a condition akin to decrement; because of this it apparently lengthens the refractory period, whereas actually it shortens it. Love[163] investigated quinidine and strophanthin. He found that they, too, produce this condition, which causes an apparent lengthening of the refractory period; actually they shorten the refractory period.

The reason why this condition resembling decrement causes an apparent lengthening of the refractory period is found in the method heretofore used in determining the refractory period. In this method the recording electrodes must of necessity be placed a short distance away from the stimulating electrodes. A test shock may excite a response in the muscle immediately beneath the stimulating electrodes, but the impulse may die out before reaching the recording electrodes, thus making it appear as though the muscle had not responded.

Lewis and Drury[164] have pointed out that these recent discoveries do not alter the main conceptions regarding the refractory period and the effects of drugs upon it, in the presence of circus movement, if we use the term "effective refractory period" instead of "refractory period." They believe, however, that the conceptions regarding fiber conduction and the partially refractory state may be altered, but that further study is needed before the discussion can be profitably continued.

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Selected Abstracts

Duperie, R., and Cantorne, G.: Le Myocarde dans L'heredo-Syphilis Precoce. Nourrisson, Sept., 1924, No. 5, 208.

This study was based on examination of the hearts of 15 congenital syphilitic infants dying during the early weeks. The myocardium was found to rank after the skin, liver and suprarenals in the frequency with which it was invaded by the spirochete. The organisms were identified in 53 per cent of the cases and in one instance the heart was the only internal organ affected. The spirochete was shown to reach the heart via the blood stream which it quickly left for the tissues. When the organisms were found in the subendocardial connective tissues, a favorite location, or in the interstitium, the morphology was preserved. In the muscle itself, however, the organisms were very long with many spirals and occupied a considerable part of the fiber.

Grossly the hearts examined were large, the muscles soft and yellowish with apical thrombi. No congenital anomalies were found. Microscopically the muscle was normal in 9 out of the 15 cases and in 6 showed pathology. The change varied from a granular condition of the protoplasm, which stained poorly but which contained the characteristic striation, to the advanced forms where striation had disappeared and the fibers seemed to have liquefied.

A proliferation of the nuclei of the sarcoplasm was also noted in these cases. In a certain number of their cases, vacuolation of the fibers was observed and this condition is discussed. The fiber had the appearance of an empty tube and around the margin was a thin protoplasmic layer of broken-down muscle fibrils. A nucleus was discernible. In less marked cases the marginal protoplasm was broader and alternating dark and clear areas were observed. The authors do not believe, with Frazer, that the condition was one of edema of the muscle, but rather hold that the appearance might be due to a persistence of a fetal state of the myocardium.

Vascular changes were extremely frequent and very obvious. The endothelium swelled up and the desquamating cells obstructed the lumen and caused thrombosis in the smaller vessels. The tunica media was in some instances involved.

Cellular reaction of the interstitium was a common finding. It varied from a mild fibroblastic reaction to the formation of strands of organized scar tissue.

The authors classify the cases into three groups, according to the apparent severity of the infection:

(a) This included the more benign cases with some inflammation of the endothelium of the capillaries, the muscle fibers and the interstitium being more or less normal.

(b) In the more severe cases the vascular changes were pronounced and involved the intima and media. Interstitial changes were slight and any alteration of the parenchyma consisted in changes in the volume of the fiber or in a slight nuclear proliferation. Spirochetes were absent or limited to the vessels.

(c) In the more marked instances generalized vascular changes with capillary thromboses were seen. Interstitial inflammation was either universal or perivascular. The muscle fibers were atrophied showing loss of striation and vacuolation was present. In such cases the spirochete was invariably demonstrable.

The massive degeneration described by Warthin was not observed nor were true gummata seen in the myocardium. No change pathognomonic of syphilis was seen in the hearts described and only the discovery of treponema could be called diagnostic. It is suggested that cases of so-called primary myocardial degeneration of the adult may in a few instances be the aftermath of a benign syphilitic myocarditis of congenital origin.

Drinker, Cecil K., Churchill, Edward D., and Ferry, Ronald M.: The Volume of Blood in the Heart and Lungs. Amer. Jour. Physiol., 1926, lxxvii, 590.

A brief discussion of the literature bearing upon pulmonary blood volume and its regulation is presented.

The method for measuring the cardio-pulmonary blood volume is described. This depends upon determining the total blood volume in a heart-lung preparation in a cat. The heart-lung preparation is novel in that the lungs are enclosed in the chest and that a new method for measuring blood flow is employed. The technic permits a continuous and simultaneous measurement of cardio-pulmonary blood volume, cardiac output and systemic blood pressure.

The cats used have had closed chests, the lungs being inflated and filling the thoracic cage and having been under artificial respiration. Cardio-pulmonary blood volumes have been measured under the following sets of conditions: (1) Cardiac inflow being constant, ventilating gas measures altered to produce (a) increase in blood carbon dioxide, (b) decrease in blood oxygen. (2) Ventilating gas mixture being constant (a) blood flow, rate and depth of artificial respiration varying. (3) Ventilation being constant (a) occlusion of left branch of pulmon-

ary artery; (b) occlusion of right branch of pulmonary artery. (4) Ventilation being constant (a) partial to complete occlusion of pulmonary veins.

There is no evidence that either increasing CO_2 or decreasing CO_2 causes more than an insignificant enlargement of the pulmonary blood volume. When oxygen lack is carried to an extreme degree, blood does slowly accumulate in the lungs. Under these conditions the left ventricle fails to meet this load before the right is seriously embarrassed. Blood may back up in the lungs to a very fair amount before pulmonary-arterial pressure is measurably increased. This fact expresses the extreme elasticity of pulmonary circulation and accounts for the accumulation of blood in the lungs when aortic discharge is reduced in the early stages of left ventricular failure.

The experiments reported constitute a further explanation of the passive position taken by the pulmonary circulation in the general phenomena of the vascular system. Increase in inflow into the right ventricle is the only means falling within ordinary experiences which results in increase of pulmonary blood volumes.

When the left branch of the pulmonary artery is occluded the right lung gives free passage to the pulmonary blood even when cardiac inflow is greatly increased. Occlusion of the right branch of the pulmonary artery indicates that the left lung is less in vascular size since diminution in aortic output appears at once.

On clamping the pulmonary veins the complete occlusion without constriction of right ventricular flow the lungs can be made to contain slightly more than double the original volume.

Carter, Edward P., and Dieuaide, Francis R.: The Influence of Changes in the Hydrogen-Ion Concentration upon the Refractory Period of the Perfused Mammalian Heart. Bull. Johns Hopkins Hospital, 1926, xxxix, 99.

The observations detailed in this study were carried out with the purpose of determining whether or not under given constant conditions of cardiac rate with a variation only in the hydrogen-ion concentration of the perfusion fluid any definite relationship could be shown to exist between the refractory period in perfused mammalian heart and the P_H of the perfusion fluid. The dog's heart was isolated, perfused and removed from the thorax by a method previously described by the authors. It was possible to exclude entirely the influence of extrinsic cardiac nerves.

It is apparent from the experiments that with a change only in the hydrogen-ion concentration of the perfusion fluid throughout so narrow a range as P_H 7.0 to P_H 7.8 there was an abrupt and significant alteration in the refractory period of both auricular and ventricular muscle

of the dog's heart, the refractory period being lengthened with the acid and shortened with the alkaline perfusate. The importance of this alteration in the duration of the refractory period in relation to re-entrant waves, circus movements and changes in the transmission interval in cardiac muscle suggests itself and is to be emphasized.

It is conceivable that in the myocardium, the seat of local disease processes in man, such marginal changes in the hydrogen-ion concentration may occur as to modify the refractory period of the tissues involved leading to disturbances in the normal sequence of events as suggested above.

Taussig, Helen B.: The Anatomy of the Hearts in Two Cases of Situs Transversus. Bull. Johns Hopkins Hospital, 1926, xxxix, 199.

This report is concerned with the anatomy of the heart in two cases of situs transversus, one in an infant and the other in an adult. In the case of the infant it was possible to make a careful dissection of the finer anatomical relations of the heart and blood vessels. In both cases it was possible to study the anatomy of the ventricles. The main gross anatomical structures and the deep muscle bundles of the ventricles presented the mirror image of the normal, while the direction of the superficial muscle bundles remained unchanged. The explanation of this peculiar anatomical relationship of the muscular layers of the ventricles is not known.

Redfield, Alfred D., and Medearis, Donald N.: The Content of Lactic Acid and the Development of Tension in Cardiac Muscle. Amer. Jour. Physiol., 1926, lxxvii, 662.

The present paper is an attempt to discover what relationship may exist between the ability of the cardiac muscle to develop tension and its content of lactic acid. For this purpose the measurement of the tension developing in the "isometric" response of a strip of cardiac muscle has proved suitable. A description of the measurement of tension in muscle strips from the ventricles of snapping turtles is given. The estimation of lactic acid is described in detail.

The ability of the ventricular muscle of the turtle to develop tension is closely correlated with its content of lactic acid.

Moore, John Walker, Hamilton, W. F., and Kinsman, J. M.: Ethyl Iodide Method for Determining the Circulation. Jour. Amer. Med. Assn., 1926, lxxxvii, 817.

Using the method of Henderson and Haggard for determining the blood flow and blood volume of the human circulation the authors found that the circulation in normal resting individuals determined by this method was much higher than that determined in the same individuals

by the Fick method. They found that combustible substances, probably ethyl iodide, seemed to return in the venous blood to the lungs. They point out certain errors in the construction of the apparatus as devised by Henderson and Haggard which do not allow the collection of the last samples of alveolar air. They also find that the assumption that ethyl iodide is destroyed during the first circulation has not been confirmed by their study. They point out that the method will have to be worked over in a very critical manner to make it applicable to the determination of the circulation in various metabolic conditions.

Spiegel, E. A., and Wassermann, S.: Experimental Studies upon the Origin of Aortic Pain and Its Conduction to the Central Nervous System. Klin. Wchnschr., 1926, v, 1569.

Experiments were performed mainly on cats, a few dogs also having been employed. Pain arising in the ascending aorta and aortic arch could be elicited by local stimuli causing acute distention of the aorta and by painting the outer wall with irritant substances. Pain could not be produced with certainty by the injection of substances which generally cause contraction of smooth muscle-containing hollow viscera, if the adventitia did not come into contact with the injection fluid. By section of various nerves, it was found that the painful impulses from the aorta were conducted over the same pathway as those arising in the heart, i.e., by way of the stellate ganglion, especially on the left side. The participation of centripetal vagal fibers could not be excluded, but in any case they play a subordinate rôle. The superior cervical ganglion could be excluded.

Keith, Norman M., and Whelan, Mary: Changes in Body Temperature and Metabolism Accompanied by Experimental Marked Diuresis. Amer. Jour. Physiol., 1926, lxxvii, 688.

Continuous records of temperature were made on dogs subjected to marked diuresis. Solutions of sugar were administered causing a loss of body water amounting to from 7 to 10 per cent of body weight with a maximal rise in body temperature of 3.4° C.

Marked hyperpyrexia did not occur in this series of experiments when care was taken to exclude all possible factors connected with the preparation and administration of the solutions of sugar. On the other hand it did occur when such toxic factors were not eliminated. A minute amount of toxic material can play an important part in causing untoward symptoms and rapid death. The authors conclude that marked rapid water loss can occur without marked hyperpyrexia. During the diuresis there is an increase in the total excretion of urea, chloride and sodium. The plasma urea, chloride and sodium are increased at the end of the diuretic period in consequence of the concentration of the blood. With restoration of water these metabolites return to normal and the excretion of urea in the urine continues.

Sollmann, Torald, and Barlow, O. W.: The Effect of Epinephrin and Prolonged Accelerator Stimulation on the Response of the Frog Heart to Stimulation of the Cardioinhibitory Nerve. Jour. Pharmacol. and Exper. Therap., 1926, xxxviii, 159.

The responsiveness of the heart to inhibitory stimulation of the vagus is increased during the perfusion of epinephrin. An entirely analogous increase of response is produced by continuous stimulation of the accelerator nerves so that it is not a specific effect of the epinephrin, for instance, on the vagus endings.

The inhibitory response becomes greater and greater the longer the epinephrin perfusion and accelerator stimulation is continued and recovers quite slowly after these are discontinued. The increased response is further the indirect rather than the direct result of augmentation, since the latter reaches its maximum very promptly and ceases at once with the end of the stimulation.

The increased response is not due to injury of the muscle by overstimulation, at least in so far as this is reflected by the systolic tone for the two curves do not correspond.

It is therefore suggested that the increase of the inhibitory response is due to the accumulation of the chemical products of the augmented muscular activity but the suggestion has not yet been put to the test.

Barlow, O. W., and Sollmann, Torald: The Effects of Epinephrin on the Response of the Frog Heart to Stimulation of the Accelerator Nerve. Jour. Pharmacol. and Exper. Therap., 1926, xxxviii, 157.

In a series of ten frogs with stimulation of the accelerator branch, ten frogs with stimulation of the vago-sympathetic without atropine, and ten frogs with stimulation of the vago-sympathetic with atropine, the authors find that a stimulation of the cardiac accelerator nerve produces little or no further augmentation in hearts which are already nearly or quite maximally augmented by epinephrin.

It is, therefore, not possible to increase the augmentor action materially by stimulating the accelerator mechanism simultaneously at the nerve and at the receptive mechanism.

McCrea, F. D., and Meek, Walter J.: The Action of Morphine in Slowing the Pulse. Jour. Pharm. and Exper. Therap., 1926, xxviii, 361.

It has long been known that the injection of morphine salts into unanesthetized dogs, after a brief period of stimulation due to nausea results in a slow, irregular heart rate, the typical "morphine pulse." The same reaction may be seen in man. The cause of the phenomenon has usually been attributed to direct stimulation of the vagus center by

the morphine. These observations led the authors to carry out experiments in an attempt to find whether the effect of morphine in slowing the heart was a direct one on the vagus center or an indirect one through the cerebrum.

After etherization and particularly decerebration the action of morphine in slowing the pulse is almost, if not entirely, abolished. This has been taken to indicate that morphine in this particular case has exerted its action on the vagal center by way of the cerebrum.

Clarke, Norman E., and Smith, F. Janney: The Electrocardiogram in Coronary Thrombosis. Jour. Lab. and Clin. Med., 1926, xi, 1071.

Three cases are reported by the authors showing changes in the electrocardiogram and suffering from coronary thrombosis, diagnosed clinically. Autopsy was obtained in one case.

In two cases the electrocardiographic change consisted of an inversion of the T-wave in all three leads. In the third case, which was autopsied, the electrocardiogram showed frequent extrasystoles, broadened QRS complex, an apical notching of the maximum deflections in Leads II and III. The most striking change was the loss of the RT interval in Lead I with the branching of the T-wave directly from the descending limb of the R-wave. In Lead III the T-wave likewise branched directly off from the S-wave definitely below the isoelectric line. The authors conclude that the electrocardiograph is of decided assistance in the diagnosis of coronary thrombosis.

Bramwell, J. Crighton, and Hickson, Sylvia K.: The Relation of the Pulse Form to Sound Production in Arteries. Heart, 1926, xiii, 109.

In this paper the authors have correlated the changes in the brachial pulse as shown by the sphygmogram with those alterations in the sounds heard over the arteries when compression is applied proximally.

The technic they employed was to apply a Riva-Rocci armlet with sufficient pressure to abolish the pulse. The pressure was then gradually diminished by allowing the air to escape. Simultaneous sphygmograph tracings were obtained and for this an open cup receiver was connected by pressure tubing to a Frank's segment capsule on which was mounted a small mirror.

The changes in the sphygmogram were constant. As the pressure fell the base line of the sphygmograph record rose at first abruptly, then more gradually. This rise, which has been attributed by Erlanger to the increased diastolic filling of the vessel, was interpreted differently by these authors, who considered it due to venous obstruction which increased the volume of the arm and so tightened the sphygmograph receiver.

The changes in the shape of the arterial wave are also constant and may be correlated with the characteristic sounds heard during the reduction of pressure. At the upper limits of the compressing pressures the sphygmogram showed a steep upstroke, preceded by a negative pre-anacrotic wave. As the pressure diminished, the negative wave increased in amplitude, then suddenly diminished and disappeared. It was this disappearance of the negative wave which corresponded with the transition between the third and fourth sounds, both the wave and the sounds occurring at similar pressures.

The reduction of the "effective diastolic pressure" seems to allow the applied pressure in the armlet to diminish the diastolic tension of the arterial wall. This in turn gives rise to an instability of the front of the pulse wave. A turbulent condition of the blood stream results with the production of rapid oscillations of pressure in the arteries. These oscillations give rise in the sphygmogram to the pre-anacrotic and anacrotic waves and are audible as the sounds heard during decompression. The Korotkow sounds may be shown to be of this nature.

Lewis, Thomas: Observations in the Regulation of the Blood Flow Through the Capillaries of the Human Skin. Heart, 1926, xiii, 1.

This study of the skin capillaries was based partly on observations of the normal skin mottling and partly on direct examination of the capillaries as shown by a magnification of 55 diameters.

Lewis' method consisted in outlining with ink a definite area on the palm of the hand and marking the contours of the minute white patches of the skin seen in the selected area. Those patches were noted to remain constant for hours at a time and even as long as a month later the general arrangement of the markings had not changed. Temperature changes, venous congestion and temporary arrest of the circulation did not appreciably alter the markings. Friction is a factor, however, which may cause temporary disappearance of a spot. The same methods were used in examining the mottling of the limbs (the cutis marmoranta). The patterns were shown to be highly resistant to changes of vascular pressure. From these two observations the author concluded that the skin is divided into anatomical areas, the appearances of which were constant.

An examination of the capillaries in selected areas of the skin was also undertaken and the position and the appearance of the capillaries and subpapillary venous plexus charted. This was carried out during normal conditions and with the venous pressure raised. It was found on repeated observations that the minute vessels were constant in number and appearance, that raising the venous pressure increased the visibility temporarily but did not materially alter the vessels.

When histamine is injected into the skin the congested area is surrounded by a paler zone, the pallor of which is due to increased tone of the minute vessels. This phenomenon is comparable with the similar effect produced by heat, freezing and other irritation of the skin where a zone of the pallor surrounds the general congested area. This arteriolar constriction has been shown to be nutritional in origin. The cells of the paler area obtained nutrient fluids from the adjacent congested area and the rate of diffusion was several millimeters in as many minutes.

From this deduction as to the rate and capacity for diffusion of vasoconstrictor and vasodilator substances, and from the constancy in the position of the observed capillaries, the author concluded that the minute vessels do not open and close continuously to supply the tissues, as has been asserted, but that the vessels are relatively constant and their vasomotor tone is the peripheral factor controlling the supplies to the tissues.

Eppinger, H., Kisch, F., and Schwarz, H.: The Influence of Muscular Exercise upon the Oxygen Saturation and the Actual Reaction of the Arterial Blood in Circulatory Diseases. Klin. Wchnschr., 1926, v, 1316.

Estimation of the oxygen saturation of the arterial blood in circulatory diseases, e.g., cardiac valvular disease, hypertensive cardiovascular disease with the patient at rest, reveals normal values almost without exception, irrespective of the presence of cyanosis, dyspnea or hydrops. Even after a certain amount of work (1000 kgm.) appreciable diminution in the oxygen saturation (hypooxemia) is noted only in a small number of instances. In chronic pulmonary diseases, e.g., emphysema, chronic tuberculosis with adhesive pleurisy, on the other hand, the oxygen saturation of the arterial blood is diminished even in the resting stage.

In those cases of circulatory disorder in which the actual reaction (P_H) of the arterial blood lies towards the acid side even when the patient is at rest, there is either diminished carbon dioxide capacity of the arterial blood, in which case it is necessary to assume the presence of acid metabolites in the blood, or there is an augmented percentage of carbon dioxide in the blood, in which case the acidification must be of pulmonary origin. The rare cases in which the P_H of the arterial blood lies towards the alkaline side are to be explained by the presence of hyperpnea which causes an increased dissipation of carbon dioxide with resulting alkalosis. After muscular exercise, the reaction of the arterial blood in circulatory disorders shifts toward the acid side in the majority of instances. The carbon dioxide capacity is generally diminished as a result of the acids formed during work. In the small number

of cases in which there is a high carbon dioxide capacity, the lowered P_H of the arterial blood is due in part at least to pulmonary causes. Hyperirritability of the respiratory center resulting in increased loss of carbon dioxide in the expired air may account for the few cases in which the reaction of the blood shifts toward the alkaline side after muscular exercise. In such cases a low carbon dioxide tension was actually found in the arterial blood following work.

Mosler, E., and Sachs, H.: Concerning the Various Forms of Ventricular Rhythm (Arrhythmia and Eurhythmia) in Auricular Fibrillation. Klin. Wchnschr., 1926, v, 1456.

The ventricular rhythm in auricular fibrillation may be either slow or rapid. In the very slow forms, the rhythm may be regular or almost so. In the very rapid forms with ventricular rates around 160 per minute, the rhythm may also appear regular. Ventricular automatism has been reported and may be due to structural disease of the junctional tissues, but auriculoventricular dissociation may also result from functional causes. The ventricular rhythms noted in auricular fibrillation and flutter are classified by the author as follows:

I. Fibrillation or flutter arrhythmia, i.e., auricular fibrillation or flutter with irregular ventricular action.
   (a) Slow form.
   (b) Rapid form.

II. Fibrillation or flutter eurhythmia, i.e., auricular fibrillation or flutter with regular ventricular action.
   (a) Slow form = auricular fibrillation or flutter with block.
   (b) Rapid form.
      1. Extremely rapid form = paroxysmal tachycardia (short or long runs) in the course of fibrillation.
      2. Moderately rapid form = blocked auricular tachysystole alternating with auriculoventricular automatism.

Petzetakis, M.: Concerning the Predominant Vagotropic Action of Adrenalin Intravenously. Arch. d. Mal. d. Coeur, 1926, xix, 513.

Healthy subjects between the ages of twenty and thirty-five were studied. The author divided the effects of intravenous doses of 1/8 mg. of adrenalin upon the cardiac rhythm into three phases: (1) period of intense acceleration, lasting from fifteen to twenty seconds (sympathetic action), (2) period of conspicuous slowing and disturbance of conduction. The latter lasts from twenty to forty seconds and represents the most conspicuous phase of the cardiac effect. The conduction changes consist of prolongation of the a-c interval in the phlebogram,

dropped beats, extrasystoles, bigeminal and trigemiral pulse (parasympathetic or vagal action) and (3) phase of total bradycardia after which the rhythm finally becomes normal. When larger doses (¼ to 1 mg.) are injected the initial period of acceleration becomes shorter and the period of disturbed conduction and bradycardia longer. Normal rhythm is restored after 15 to 30 minutes.

According to Danielopolu, very small doses produce only parasympathetic effects, whereas the larger doses act on both the sympathetic and parasympathetic (vagal) fibers, but predominantly on the former. The observations of the author however lead him to the conclusion that the larger doses of adrenalin (⅛ to 1 mg.) are amphotropic, but act predominantly on the parasympathetic. The vagotropic action, which is abolished by atropine, explains the conspicuous slowing and the disturbances of conduction.

The author calls attention to the possible dangers of intracardiac injections of adrenalin. Fatal syncope may result especially when chloroform anesthesia has been administered. He advises the use of other methods to resuscitate the heart, but if these fail the injection of adrenalin in relatively small doses (1/10 to 1/16 mg.) to avoid the harmful vagotropic effects of the drug. A second dose may be given if necessary, not to exceed ½ mg. He also believes that caution must be exercised in the use of adrenalin in the treatment of Adams-Stokes disease.

Leibowitz, O.: A Contribution to the Extracardiac Action of Digitalis. Klin. Wchnschr., 1926, v, 1428.

In a case of persistent auricular fibrillation with congestive failure, glycosuria (1.3 per cent) and acetonuria developed after digitalis medication and ceased two days after the drug was discontinued in spite of a diet rich in carbohydrates. Several months later when there were no longer signs of cardiac failure, the administration of digitalis caused the blood sugar to rise from 0.068 per cent to 0.12 per cent without, however, inducing glycosuria. The author, who is continuing his investigations concludes that digitalis may have a toxic effect on the carbohydrate metabolism even though it influences the circulation in a beneficial manner.

Lindhard, J.: A Dye Method for Determining the Blood Volume in Man. Amer. Jour. Physiol., 1926, lxxvii, 669.

The author points out that it is absolutely essential that the blood of the subject is completely mixed with the dye injected, by a suitable routine of movements. He has studied vitol red and congo red but concludes that congo red is unsuitable.

The total blood volume of 11 healthy male subjects is found to be on an average 4.9 per cent of body weight with individual variations rang-

ing from 4.2 to 5.9 per cent. Double determinations on the same subject agree within 0.2 liter.

When dye substances are injected repeatedly the subject after some few injections acquires the property of eliminating the dye from the circulation, thus rendering further application of the method illusory.

Howell, W. H.: Note upon the Presence of Heparin in Normal and Hemophilic Blood in Man. Amer. Jour. Physiol., 1926, lxxvii, 680.

The author describes a method for detecting the presence of heparin in blood from peptonized dogs. The same method is used for detecting the presence of heparin in human blood.

The fact that the heparin in the uncoagulable blood from the peptonized dog as tested by these methods is greatly increased suggested the possibility that the delayed clotting of hemophilic blood may be due to the same cause. Two young men belonging to the hemophilic families which the author studied in 1914 were used in these experiments. The results were not consistent. In some cases the hemophilic blood contained greater amounts of heparin than the normal blood judged by the two tests described while in other cases it contained practically the same amount or even less. The hemophilic blood seemed to vary in its content of heparin but there is no clear indication of a greater quantity. The results therefore indicate that the delayed coagulation cannot be explained on this ground.

Escudero, P.: The "Black Cardiacs" and Ayerza's Disease (Critical Review). Arch. de Mal. d. Coeur, 1926, xix, 439.

In 1901 Ayerza described under the designation of "black cardiacs" a syndrome characterized by cardiac hypertrophy predominantly in the right ventricle, polyglobulism and intense cyanosis of the face and extremities. In 1905 Escudero studied the anatomical lesions which consisted essentially of right ventricular hypertrophy and generalized atherosclerosis of the pulmonary artery. In 1911 he noted the coexistence of pulmonary sclerosis and bronchial syphilis. Until 1922, Arrilaga considered the sclerosis of the pulmonary artery to be secondary to chronic lesions of the lung, especially chronic bronchitis, but since 1922 he has believed the sclerosis of the pulmonary artery to be syphilitic in origin and the primary lesion in Ayerza's disease, not necessarily associated with pulmonary lesions of any kind. One of Arrilaga's patients died in Escudero's clinic. At autopsy there was bronchial syphilis with peribronchial sclerosis, generalized bronchiectases, sclero-gummatous syphilis of both lungs and sclerosis of the pulmonary artery, especially of the finer branches.

Escudero describes the evolution of the disease as occurring in two periods: (1) the bronchial period and (2) the cardiac period. In the

bronchial period, there are signs of bronchial syphilis and polycythemia. In the cardiac period, there are in addition cardio-arterial symptoms consisting of hypertension in the pulmonary circuit, hypertrophy of the right ventricle and auricle with integrity of the general circulation, and moderate or intense erythrosis (cerise color of the skin), associated with a high red blood cell count, and when the right ventricle fails erythrocyanosis and finally intense cyanosis. Ayerza's disease must be distinguished from sclerosis of the pulmonary artery secondary to chronic pulmonary disease and mitral stenosis, primary sclerosis of the pulmonary artery, and the Osler-Vaquez disease. According to Escudero, bronchial syphilis is at the bottom of the disease, but whether the obliterative sclerosis of the pulmonary artery is of the ordinary atherosclerotic type or, as Arrilaga believes, is due directly to syphilis he leaves an open question.

Eustis, Allan: The Dweight-Frost Cardio-Respiratory Test as an Aid in the Early Recognition of Myocardial Insufficiency. South. Med. Jour., 1926, xix, 585.

The author has used the test in twenty-five apparently normal individuals and in a group of one hundred other cases with symptoms of cardiac disease. He states that in his practice the test has been of considerable value in estimation of the reserve power of the heart muscle.

Pratt, Joseph H.: Cardiac Asthma. Jour. Amer. Med. Assn., 1926, lxxxvii, 809.

The author defines cardiac asthma as a paroxysmal dyspnea developing suddenly while the patient is at rest, accompanied by a sense of suffocation and occurring in organic heart disease. The attacks of dyspnea are often associated with the definite signs of acute cardiac weakness. He analyzes a series of 366 cases seen in private practice; 313 of these cases showed organic heart disease. He excludes paroxysms of breathlessness brought on by exertion and attacks of increased dyspnea in orthopneic patients with advanced heart failure.

There were 39 patients with a history of paroxysmal dyspnea with oppression and signs of suffocation which he regards as examples of true cardiac asthma. Thirty-six of these cases were in patients in whom the diagnosis of senile heart or cardiosclerosis was made. Only two of the cases were in patients with rheumatic heart disease. Both had aortic insufficiency. There was one case of syphilitic aortitis but there were only five cases of syphilitic heart disease in the entire series of 366 cases.

The author divides cardiac asthma into four groups (1) Pure cardiac asthma. (2) Cardiac asthma with angina pectoris. (3) Cardiac asthma

with pulmonary edema. (4) A combined form of cardiac asthma with both angina and pulmonary edema.

Benefit in attacks has apparently been obtained sometimes from nitrites, epinephrin and caffein sodium benzoate. Morphine given subcutaneously in a goodly dose is by far the best remedy for a severe attack.

Shapiro, Shepard: The Basal Metabolic Rate in Cases of Chronic Cardiac Disease and in Cases of Hypertension. Arch. Int. Med., 1926, xxxviii, 385.

The author has studied the metabolic rates obtained under basal conditions in a series of 42 cases of heart disease, including 22 patients with valvular lesions, 15 cases with hypertension or cardiac hypertrophy, 2 with congenital heart disease and 3 with functional tachycardia. Of the 42 patients studied, the heat production was found to be definitely elevated above normal in 3 cases. These patients all had dyspnea or hyperpnea which the author believes was responsible for the increased metabolism. In the remaining 39 cases he found that organic heart disease unaccompanied by dyspnea at least does not elevate the basal metabolism. He has observed increased basal metabolism in a series of patients with true hypertension who did not have exophthalmic goiter and who were not dyspneic at the time the metabolic rates were determined.

Alvarez, Walter C., McCalla, R. L., and Zimmermann, A.: Hypertension and Constipation: A Statistical Inquiry. Arch. Int. Med., 1926, xxxviii, 158.

In this study the authors analyze the records of four hundred and ten men and five hundred and eighty-five women seen in private practice. Of these four hundred and thirty-six were classed as normal, four hundred and fourteen as habitually constipated and one hundred and ten as having occasional or recent constipation, and thirty-five as having diarrhea.

An analysis of the table shows that in men constipation has absolutely no effect on the blood pressure; in women there is a pretty definite connection between constipation and a slightly lowered mean blood pressure. It is possible that diarrhea is also associated with a lower pressure, but the data are too few for a trustworthy conclusion.

Some of the believers in intestinal poisoning may assert that the blood pressure has been lowered in the constipated group by histamine-like toxins but that will not explain why it did not happen in the men. Another difficulty in interpretation arises from the fact that one might

just as well argue that hypertension has perhaps a slightly laxative effect on women. This is not at all improbable. There may be certain conditions, which, while not laxative enough to produce diarrhea, are laxative enough to insure a high percentage of individuals who have normal bowel movements.

Winogradoff, W. W.: Concerning the Significance of the Alfred de Musset Sign in Heart Disease. Klin. Wchnschr., 1926, v, 1467.

It is generally stated that the Alfred de Musset sign, which is a rhythmic (pulsatile) jerking movement of the head, is characteristic for aortic insufficiency and aortic aneurysm. The author, however, found this sign also in tricuspid insufficiency, especially in the relative or functional variety. The movement of the head is less pronounced than in the aortic cases, but is usually seen without difficulty. It is often best observed by watching the movement of the hair and at times may be best seen from behind. The anteroposterior movement of the head is not so conspicuous as in aortic insufficiency, the amplitude being smaller and the motion more circular, with a large number of smaller vibrations. The presence of this sign speaks for relative tricuspid insufficiency with positive venous pulse and generally auricular fibrillation. Its disappearance usually indicates diminished distention of the right ventricle and auricle, return of the venous pulse from positive to negative and the restoration of normal rhythm. The sign is less frequently encountered in organic tricuspid insufficiency.

Coombs, Carey F.: Cardiac Symptoms of Pernicious Anemia. British Med. Jour., 1926, July 31, p. 185.

The author points out the two important facts in the course of pernicious anemia which have some clinical significance: (1) the simulation of cardiac disease by pernicious anemia in its early stages; the shortness of breath, slight cyanosis and anemia suggest an early myocardial degeneration. (2) Among the symptoms of myocardial disease sometimes exhibited by the patient with pernicious anemia, cardiac pain has a place. Eight of the author's thirty-six patients complained of it.

Kahn, Morris H.: Prodromal Symptoms in Angina Pectoris. Amer. Jour. Med. Sci., 1926, lxxii, 418.

In an analysis of 82 patients with angina pectoris who have been under careful observation the author calls attention to certain prodromal symptoms and prodromal attacks that eventually present the unmistakable features of the disease. These prodromal symptoms he divides into several groups: (1) Prodromal attacks simulating angina pectoris. In four cases the attacks of angina pectoris were preceded by symptoms which do not bear the characteristics of angina. In these

cases the first attack indicated some sudden cardiac change and consisted of sudden weakness, faintness and darkness before the eyes, falling to the ground without loss of consciousness and without chest pain.

(2) Substernal burning sensation. Four cases are cited to illustrate the burning sensation or pain behind the sternum. He assumes this to be a warning signal in questionable cases.

(3) Epigastric pressing or burning sensation. The pain preceding typical attacks is in some cases located in the epigastrium. These symptoms often focus attention to the stomach, sometimes for a long period before the actual condition is discovered.

(4) Dyspnea, palpitation and fatigue on moderate exertion. In some cases for a more or less prolonged period there was noted a degree of limitation of function usually only mild with shortness of breath on exertion and palpitation at times.

(5) Cardiac asthma with pulsus alternans. In three cases of this series the symptoms were predominantly those of cardiac asthma. The asthma in one case developed two years after the occurrence of typical attacks of angina pectoris.

(6) Cerebral thrombosis. In four cases of the series cerebral thrombosis with hemiplegia was associated with angina pectoris. In two of the cases the cerebral thrombosis preceded the anginal symptoms.

The author points out that the pathological process which eventually produces the symptoms of angina pectoris is a prolonged one; that there is early involvement of the aorta and coronary arteries long before the anginal symptoms develop. It is therefore important in the prevention of angina pectoris to give careful study and attention to these premonitory symptoms.

Kahn, Morris H.: Etiologic Factors in Angina Pectoris. Amer. Jour. Med. Sci., 1926, lxxii, 195.

The etiologic factors are discussed in 82 cases of angina pectoris seen in private practice. Almost 25 per cent of the cases had their first typical attack before the age of forty years. Sex proportion was 65 males to 16 females. Tobacco and alcohol could not be excluded as contributory factors. Sudden excessive strain is the most important immediate factor preceding the attack and its effect is more likely to be injurious to the individual engaged in moderate or sedentary occupations in whom the heart and aorta have not been trained to accept sudden strain adaptably. Acute infectious causes such as rheumatism and infected tonsils appear to be important in initiating vascular changes in the aorta and coronary artery area. In only 3 cases was syphilis a factor. Diabetes was present in ten cases of angina pectoris. There was no true etiologic relationship between arterial pressure and the attacks. Gall bladder disease coexisted in 3 cases.

Boyd, William: Acute Myocardial Syphilis. Arch. Path. and Lab. Med., 1926, ii, 340.

The present communication deals with what appears to be another example of sudden death due to an exacerbation of latent myocardial syphilis, described by Warthin. Following Warthin's description, the author reports a case showing at autopsy in the heart muscle collections of lymphocytes and plasma cells here and there in relation to the blood vessels. Similar collections were found in the adventitia of the left coronary artery. In addition peculiar collections of polymorphonuclear leucocytes were found in the interstitial tissues of the wall of the left ventricle. Sections were stained by Warthin's modification of the Levaditi method and collections of spirochetes were found in the acute inflammatory lesions. The patient was a woman.

Means, J. H., White, P. D., and Krantz, C. I.: Observations on the Heart in Myxedema. Boston Med. and Surg. Jour., 1926, cxcv, 455.

In a series of 48 cases of myxedema seen in the thyroid clinic of the Massachusetts General Hospital in the last 12 years the authors find two cases which show signs of disturbances in the heart. These results would seem to justify the conclusion that "myxedema heart" is far from common. One of the two cases showed a moderate cardiac dilatation subsiding rapidly under thyroid treatment. The second case showed symptoms of angina pectoris. There was a clear relationship between the amount of thyroid given and the frequency and severity of the anginal attacks. With no thyroid the patient was myxedematous and free from angina. When sufficient thyroid was given to bring him to a normal metabolic plane he suffered from angina. It seems fair to conclude that the increased blood flow through the heart was directly responsible.

Kreidler, Wm. A.: Bacteriological Studies in Endocarditis. Jour. Infect. Dis., 1926, xxxix, 186.

It was the purpose of this study to search for distinctive features in the group of streptococci associated with Streptococcus endocarditis. Fourteen cases are described which were typical of the disease. In a relatively high percentage a streptococcus could be isolated from the blood; and also frequently from vegetations on heart valves and infarcts in cases coming to necropsy. All but one yielded an organism producing green colonies on blood agar. In the one exception a typical beta-hemolyzer was isolated.

Cultivation of organisms in collodion sacs in the peritoneal cavities of rabbits did not change their morphological or cultural characteristics or their serological reactions. There occurred no cross agglu-

tination, cross precipitation or cross complement fixation among the strains isolated. It appears impossible to group these streptococci on the basis of their serological reactions.

Lesions of the heart valves similar to those occurring in human beings can be produced experimentally in animals by injection of these organisms directly into the heart and intravenously.

The cases reported were adults varying in age from twenty to fifty-eight years. One child of fifteen years is included. A history of rheumatic fever or tonsillitis was present in nearly every case. No description of the heart at autopsy is given.

Wood, J. Edwin, Jr., Jones, T. Duckett, and Kimbrough, Ray D.: The Etiology of Heart Disease: A Clinical Study of 623 Cases with Certain Observations on Race and Climate. Amer. Jour. Med. Sci., 1926, clxxii, 185.

Two series of cases of organic heart disease are presented for comparison. Series I included 300 cases admitted to the Medical Service of the University of Virginia Hospital from Oct. 1, 1925, to Jan. 1, 1926. Series II comprised 323 cases admitted to the Medical Service of the Massachusetts General Hospital from March 19, 1924, to Nov. 1, 1924.

From a study of the tables the authors conclude that heart disease is decidedly more common in the negro than in the white. It appears that the ratio is almost two times as frequent in the negro. It is interesting to note that hypertensive and syphilitic heart disease are in the main responsible for the increased incidence of heart disease in this race. Males preponderate distinctly in the colored syphilitic heart disease group.

Rheumatic heart disease of all types is almost two times as common in Massachusetts as in Virginia, according to this study. The two series tend to show that rheumatic heart disease shows a gradual increase in occurrence from South to North in the Eastern part of the United States.

Angina pectoris is less common in the negro than in the white despite the fact that syphilitic arteriosclerosis is such an important factor in the former.

Mackie, Thomas T.: Rheumatic Fever. Amer. Jour. Med. Sci., 1926, lxxii, 199.

The basis of this study comprises 393 cases of rheumatic fever taken from the records of the Presbyterian Hospital in New York and comprise consecutive admissions over a period of nine years with the exception of scattered cases excluded because of incompleteness of

history or work-up. The types of rheumatic fever include acute, subacute and chronic forms. A group of 89 patients with chorea was studied at the same time. There is an approximately equal distribution between the two sexes of the rheumatic group. The chorea group, on the other hand, shows a marked predominance of females,—58 as compared to 31 males.

Age of Onset of First Attack.—Rheumatic fever shows a somewhat irregular curve of the incidence, rising from 4.7 per cent under the age of five years to a peak of 20.8 per cent between the ages of ten and fifteen years; thereafter it slowly but progressively falls to 1.5 per cent between the ages of fifty and fifty-five years. The influence of chorea, however, is seen to be present during a much shorter period. Starting with an initial incidence of 1.1 per cent, its curve rises steeply to a maximum of 58.4 per cent between the ages of five and ten years, falling rapidly then to an incidence rate of 7.8 per cent between the ages of fifteen and twenty years, after which period no initial attacks were found.

Incidence of Cardiac Involvement in the First Attack.—Of the 366 cases of rheumatic fever, 250, or 68.3 per cent, showed evidence of cardiac disease either at the time of admission to the hospital or during their stay in the wards. In 42 of 204 cases in the follow-up clinic the cardiac condition was definitely improved. On the other hand, 57 cases showed evidence of a progressive lesion and 103 cases were found to be essentially unchanged. Of 66 cases of chorea similarly analyzed, 34 had definite signs of cardiac involvement on admission or during their stay in the hospital. Forty of these individuals were subsequently seen in the follow-up clinic and 11 showed improvement in the cardiac condition, while 8 had progressing lesions. Twenty-one cases of this group were found to be unchanged.

The incidence curve of cardiac involvement in the first attack of rheumatic fever as found in this series approximately follows that of the age of onset of rheumatism.

The Rôle of Focal Infection.—That focal infection plays a rôle in the etiology seems apparent from the comparison of its occurrence in the rheumatic cases with a series of 400 nonrheumatic controls. In the former group it was found in 80 per cent of the individuals as against 66 per cent in the latter group. Tonsillar infection was found to be more than twice as prevalent in the rheumatic fever cases as in the controls.

The complete removal of the tonsils and evidence of infection that was present, together with appropriate treatment of other foci of infection, seems to reduce but not to remove the incidence of recurrences of rheumatic fever.

Recurrences of Rheumatic Fever.—Two hundred fifty-two cases were available for analysis concerning this point. Seventy-one per cent irrespective of age had at least one recurrence. Age, too, has an important bearing upon the development of the disease. Of 87 cases comprising the adult group, 58.6 per cent had recurrences. In the younger group of 165 individuals 78.2 per cent had at least one return of rheumatic fever. Those cases occurring between five and ten years of age present the peak of the incidence rate of recurrence. Of 45 patients between these ages 93.4 per cent had a return of the acute phenomena. An attempt to ascertain the average time interval between initial attack and first recurrence revealed the surprising fact that only 57 per cent had the first occurrence within four years after the primary episode. It would appear, therefore, that it is only after the lapse of three years of complete freedom from symptoms that an individual has better than an even chance of escaping a further bout with acute rheumatic fever.

The importance of prolonged and careful observation of patients with rheumatic heart disease during periods of quiesence is not generally appreciated. The necessity for prolonged rest under medical care in suitable surroundings is not realized. A community which provides so well for the arrest of tuberculous disease and the rehabilitation of the patient offers no help to the victim of rheumatism until the late stages of the disease have supervened and the road to health and economic independence is closed. Further attacks upon the problem of rheumatic infection must be directed not only to the discovery of the etiology of the disease but to the education necessary to provide the means for its adequate and successful treatment.

Hartman, Henry, and Levy, M. D.: Rupture of Aortic Aneurysm into the Superior Vena Cava: Report of Two Cases. South. Med. Jour., 1926, xix, 595.

The authors report two cases of sacular aneurysm with a rupture into the superior vena cava. In one there was present a syphilitic aortitis and valvulitis; the other showed chronic diffuse nephritis with pericarditis and pleurisy. Autopsy was obtained in both cases.

Lehman, W.: Clinical and Bacteriological Observations upon Endocarditis Lenta. Klin. Wchnschr., 1926, v, 1408.

Lehmann, working in Schottmueller's clinic, claims that the clinical picture of endocarditis lenta is sharply defined and due exclusively to the Streptococcus viridans. Though a variety of other organisms, e.g., staphylococcus, Influenza bacillus, Streptococcus hemolyticus, pneumococcus, diphtheroid bacillus, have been reported as etiological agents by other authors, none of these were found in Schottmueller's

clinic. The author states that the diplococcus crassus and the Staphylococcus aureus or albus are frequently encountered as contaminating bacteria in blood cultures, and that those who isolated hemolytic streptococci have generally failed to recognize the fact that the Streptococcus viridans may possess hemolytic properties under certain circumstances. In other cases the streptococci isolated are true hemolytic streptococci, but are merely secondary invaders. He believes that the case for mutation between nonhemolytic and hemolytic streptococci is not proved. In recent years, authors reporting negative blood cultures in an unusually large percentage of cases have expressed the opinion that the character of the disease is changing, but Lehmann replies that from 1922 to 1925 he obtained positive cultures of streptococcus viridans in 20 of 22 cases and that the disease has not changed.

Reiche, F.: Paralysis of the Left Recurrent Nerve in Mitral Stenosis. Med. Klinik, 1926, xxii, 1142.

Paralysis of the left recurrent nerve is a comparatively rare complication of mitral stenosis, less than eighty cases having been reported. The author observed this complication twice in 300 cases of mitral stenosis. At autopsy in one of his cases, the greatly dilated left auricle had compressed and pushed aside the pulmonary artery so that it impinged directly upon the aorta and recurrent nerve, the upper portion of which was grayer than normal and greatly reduced in size. The compression of the pulmonary artery did not give rise to murmurs as in Carrau's case.

Lutembacher, R.: Coronary Arteritis and Arteritis of the Pancreas. Disturbances of Conduction and Diabetes. Arch. d. Mal. d. Couer, 1926, xix, 522.

A diabetic male developed symptoms of coronary artery disease at the age of thirty-seven years and fifteen years later (1921) began to have attacks of Adams-Stokes disease. When examined in 1921, the pulse was 26 per minute and the electrocardiogram showed 2:1 block alternating with 1:1 rhythm, with lengthening of the P-R interval and changes indicative of disturbed conduction in the left branch of the bundle. In spite of a negative blood Wassermann test, antisyphilitic treatment was instituted because of suspected hereditary syphilis The auriculoventricular dissociation disappeared, but the left bundle-branch block persisted. The glycosuria also improved and finally disappeared. Death occurred suddenly two years later.

At autopsy there were old infarcts in the interventricular septum and in the muscle supplied by the anterior descending branch of the left coronary artery, which showed conspicuous sclerosis and narrowing of the lumen. The pancreas showed "arteritis" with complete

obliteration of some of the smaller branches and extensive necroses of the parenchyma. The author considers the changes in the coronary and pancreatic arteries to be syphilitic, but the evidence is not convincing. He attributes the disappearance of the auriculoventricular block to improved virigation of the upper portion of the His bundle consequent upon the antisyphilitic therapy and the disappearance of the glycosuria to the improved blood supply in the pancreas. The antisyphilitic treatment, which he feels was instituted too late and discontinued too soon, did not efface the severe structural changes in the coronary arteries which finally caused death by sudden ischemia of the ventricular center.

Frommel, E., and Thévenod, A.: A Complete and Transient Auriculoventricular Block in the Course of a Pneumonia. Arch. d. Mal. d. Coeur, 1926, xix, 528.

A case of heart-block is reported which developed during the course of a protracted pneumonia in a man of seventy-eight years. When discovered the auriculoventricular dissociation was complete, but several days later became incomplete and finally disappeared. Digitalis had been administered prior to the appearance of the block, and a second course was given after the rhythm became normal to test the effect of the drug. A 2:1 block developed. The authors conclude that the pneumonia played a minor rôle in the production of the abnormal rhythm.

Lutembacher, R.: Coronary Arteritis and Subendocardial Infarction with Embolic Phenomena. Arch. d. Mal. d. Couer, 1926, xix, 505.

The author reports two autopsied cases of subendocardial myocardial infarction with fibrosis and thrombus formation at the site of the scar and sclerosis of the smaller coronary arteries. In both there were embolic phenomena due to the mural thrombosis in the left ventricle. The author emphasizes the significance of changes in the electrocardiogram for the detection of subendocardial disease. In Case I there were not only spontaneous variations in the electrocardiogram, but changes could be induced by acceleration of the heart rate in response to exercise, change from the decubitus to the erect posture, ocular compression or the administration of amyl nitrite. The following abnormalities are described: prolongation of the P-R interval, widening of the QRS complex and notching of the R-wave in all leads, auricular extrasystoles followed by modified or unmodified QRS complex, spontaneous change of the R-wave in Lead I from inverted and smooth to upright and notched. The electrocardiograms also showed diphasic as well as completely inverted T-waves, and whether positive or negative the T-wave pointed in the direction opposite to that of the corresponding R-wave.

Smith, Fred M., Graber, V. C.: Coronary Thrombosis with Congenital Absence of the Left Coronary Artery. Arch. Int. Med., 1926, xxxviii, 222.

A case of coronary thrombosis is reported occurring in a man in whom there were no clinical manifestations of myocardial weakness prior to the cardiac accident.

The anomaly of the coronary circulation was very unusual. The blood supply to the entire heart was furnished by one large artery which during its early course corresponded in location with that of the right coronary artery. Later branches were given off which reconstructed in a diminutive manner the descending or circulatory branches of the left coronary artery. The blood supply to the left ventricle was much less than in the normal subject. It was difficult to understand how the blood supply in this instance permitted the individual to perform such heavy physical work. It is possible that the blood supply derived directly from the left ventricle cavity might have compensated for the apparent deficiency in the main coronary vessels.

The area of infarction was confined to the left ventricle and the changes in the electrocardiogram were similar to those produced experimentally by the ligation of branches of the left coronary artery at its source following the occlusion of corresponding arteries in man.

Duncan, Garfield G., and Rudy, Abraham: Myocardial Insufficiency Following Arterial Hypertension; Its Prevention and Treatment. Amer. Jour. Med. Sci., 1926, clxxvii, 351.

Ten cases of myocardial insufficiency were selected which proved refractory to standard treatments of digitalis and other drug therapeutic procedures. The patients were placed on a diet in which the salt content was reduced to a minimum. As a result there was a fall in blood pressure in every instance. There was a decrease in the diastolic pressure in every instance, though satisfactory levels were assumed in only six. The authors conclude that the dietetic results seem to provide a most powerful means of preventing and controlling myocardial insufficiency which is secondary to arterial hypertension.

Leas, Roscoe D., and Thatcher, Harvey S.: Mycotic Aneurysm. A Report of Two Cases. Arch. Int. Med., 1926, xxxviii, 226.

The cases in this report are of particular interest because they offer suggestive clinical evidence as to the mechanism of the formation of a mycotic process and illustrate the probable cause of pain in such a condition. Clinical evidence also suggests that the pathological process is the same in arteries and veins and differs only in the end-result.

The first case may be summarized as one of bacterial endocarditis with hemolytic streptococcus septicemia, in proof of which there was a positive blood culture, evidence of endocardial and myocardial involvement, embolic phenomena and a mycotic aneurysm. The aneurysm involved the superior mesenteric artery.

The second case was one of bacterial endocarditis with Streptococcus viridans septicemia, proof of which was a positive blood culture, evidence of endocardial involvement, embolic phenomena and a mycotic aneurysm in both the superior mesenteric artery and the aorta.

Smith, Fred M., and Hansmann, G. H.: Mycotic Aneurysm of the Aorta. Arch. Int. Med., 1926, xxxviii, 367.

The case here reported was that of a boy seventeen years of age, who had the typical clinical manifestations of subacute bacterial endocarditis in which the Streptococcus viridans was the responsible organism. Even though the course was fatal, the termination was hastened by the rupture of a mycotic aneurysm.

The aorta was mottled by the early lesions of arterial sclerosis. At the site of the opening of the ductus arteriosus during embryonic life, the aorta was constricted to less than half of the normal size. One centimeter below this constriction there was an opening into the wall of the aorta approximately 3 cm. in diameter. This opening connected with an aneurysmal sac 6 cm. in diameter which projected into the left chest. It was filled with an antemortem clot. The aneurysm had ruptured into the left chest cavity.

Lewis, Dean, and Reichert, F. L.: The Collateral Circulation in Thromboangiitis Obliterans. Jour. Amer. Med. Assn., 1926, lxxxvii, 302.

Roentgenograms of vessels in thromboangiitis obliterans injected with bismuth oxychloride reveal an extensive collateral circulation and indicate that gangrene in these cases is due to the inability of the collateral circulation to keep ahead of the advancing thrombus. An attempt may be made to hasten the development of a collateral circulation by division of the femoral artery just distal to the origin of the perfunda femoris. Division of this artery throws out of function the principal arteries involved in the chronic inflammatory process. That thromboangiitis obliterans does not interfere with the development of a collateral circulation is indicated by visualization of vessels in these cases.

The early and practically complete relief from pain following division of the femoral artery suggests that spasm of the artery may be an important factor in causing pain and that throwing out of function all the arteries principally involved in this process will be an important factor in relieving pain.

Otto, Harold L., and Gold, Harry: Persistent Premature Contractions. Arch. Int. Med., 1926, xxxviii, 186.

This article is a report of results obtained in a careful study of premature contractions with particular regard to its reaction to the drugs most commonly used in the treatment and study of heart disease. Twelve cases were studied under controlled conditions while in the hospital. Rest in bed and atropine had no effect on the number of premature contractions. Exercise and epinephrine increased the number. Quinidine, quinine and digitalis decreased the number. These results appeared to be quantitatively, but not qualitatively constant and unrelated to the type of premature contraction or the etiological, anatomical or functional type of heart disease in which they occurred.

References are commonly made in the literature to the beneficial effects of the withdrawal of coffee, tea, tobacco and alcohol, etc., in patients with premature contractions. Undoubtedly such measures do diminish or abolish premature contractions. There is, however, a large group of patients in whom such measures are without effect. Quinine appears to be the least satisfactory drug because of the large dosage necessary and the early supervention of cinchonism. With quinidine the results are better but the tendency of the premature contractions to "escape" demands increasingly larger doses. The results of their study indicate that both of these drugs have a limited field of usefulness in the treatment of patients with premature contractions, and furthermore that digitalis deserves a more prominent place in the treatment of the premature contraction than it has heretofore received.

Williamson, Charles Spencer, and Ets, Harold N.: The Rationale of Therapeutic Puncture in Pericardial Effusion. An Experimental Study. Arch. Int. Med., 1926, xxxviii, 206.

The authors relate four patients in whom, according to their opinion, pericardial aspiration or a more complete removal of the fluid might have delayed or prevented the death of the patient. The type of death in each of these individuals they describe as being precordial in nature.

With this in mind experiments on dogs were undertaken to determine the amount of fluid present in the pericardial sac which is necessary to cause stoppage of the heart. Changes of continuous pressure, of arterial and central venous pressures and the pressure of fluid introduced into the pericardial sac are illustrated by kymograph record of blood pressure. The tracings show that a rather gradual rise of the intrapericardial pressure has for its invariable result the raising of the venous and the lowering of the arterial pressure. It may be so

seen that for a given increment in the pericardial pressure, these changes are more pronounced as this pressure becomes higher, so that as it approximates that which obtains in the vena cava, i.e., as it nears the point at which the circulation stops, the rise in the venous and the drop in the arterial pressure is most noticeable. That these phenomena are due to the increase in pericardial pressure alone is evident from the fact that even a partial release of it causes the venous pressure to drop and the arterial to rise immediately.

The authors conclude that, in clinical practice, measurements of the arterial pressure as carried out at the bedside enable one, in a general way, in cases of pericarditis substantially uncomplicated, to prognosticate an increased pressure in the pericardium. A steady fall in the arterial pressure and especially a sudden increase in the rate of fall indicates a near approach to the critical point and calls for a therapeutic puncture.

Reed, C. I.: Heparin. III. Effect on Coagulation Time when Added to Blood after Clotting Has Begun. Am. Jour. Physiol., 1926, lxxvii, 568.

Amounts of blood were withdrawn from rabbits and dogs and placed in a series of small test tubes. At varying intervals of time after withdrawal heparin was added in concentration of 0.001 gm. to 1 c.c. blood.

It is apparent from these experiments that whatever the mechanism of action of heparin, even after the process of coagulation has begun, the addition of small amounts of heparin may prolong coagulation time to a marked degree or even arrest the process entirely.

Serby, A. M.: The Pharmacology and Therapeutics of Novasurol. Arch. Int. Med., 1926, xxxviii, 374.

In this report six cases of marked cardiac decompensation were studied. One cubic centimeter of novasurol intramuscularly or intravenously two times weekly caused profuse diuresis and persistent edema. Diuresis appears three hours after administration. It lasts twelve hours in young individuals and twenty-four to forty-eight hours in elderly or weak individuals. In some cases novasurol may not cause diuresis although not producing any renal damage. It may induce a decrease in edema and an increase in uremia simultaneously. It may cause renal damage and should not be used in the face of nitrogen retention or rapid urinary output.

Book Reviews

HERZKRANKHEITEN BEI FRAUEN.—By Prof. N. Jagic. Urban and Schwarzenberg, Berlin and Vienna, 1926. Pp. 103.

In this monograph are considered the usual forms of heart disease which occur in both sexes, but special emphasis is laid upon the circulatory disturbances which arise during pregnancy and the menopause and upon those cardiac conditions which are more common in women than in men. Six pages are devoted to the differential diagnosis between chlorosis and organic mitral insufficiency and myocardial disease; thyrotoxic disturbances and the indications for the interruption of pregnancy are treated rather more fully than the remaining sections, which are brief. A number of interesting clinical observations are recorded, but on the whole there is very little of importance in the monograph which is not satisfactorily treated in the standard textbooks of cardiology and obstetrics. A brief bibliography is appended, but there are no references to American or English publications.

B. S.

NEUE KLINISCHE GESICHTSPUNKTE ZUR LEHRE VOM ASTHMA CARDIALE.—By Dr. Sigmund Wassermann. Urban and Schwarzenberg, Berlin and Vienna, 1926. Pp. 168.

Wassermann's monograph on cardiac asthma originally appeared in the *Wiener Archiv für Innere Medizin* for January, 1926. The author opposes Traube's theory that cardiac asthma is due to pulmonary stasis secondary to failure of the left ventricle and that of Hoffmann and Hess that it is due to reflexes from the heart. Wassermann believes that the attacks are caused by insufficiency of the left ventricle, the result of which is anoxemic stimulation of the respiratory center. The failure of the left ventricle is purely functional and has nothing to do with manifest failure or with retrograde stasis in the lungs. That pulmonary stasis does not play a rôle is shown by the fact that typical cardiac asthma does not occur in uncomplicated cases of mitral stenosis (in which pulmonary stasis readily develops). On the other hand, this form of paroxysmal dyspnea occurs almost exclusively in cases in which the left ventricle is predominantly affected, the chief of these being aortic insufficiency and occlusion of the left coronary artery.

The "asthmatic" seizures are accompanied and often preceded by anxiety, thoracic oppression, and a sense of suffocation or strangulation and sometimes by thoracic or cardiac pain. These symptoms are primarily of central origin and cannot be explained by pulmonary stasis. In certain cases the dyspnea is of the expiratory type, due apparently to bronchoconstriction of central origin. Other phenomena resulting from anoxemic excitation of the medullary and other centers are bradycardia, pharyngeal spasm (feeling of suffocation),

paroxysmal hypertension, nausea and other gastrointestinal disturbances and frequency and urgency of micturition. According to Wassermann, the psychomotor unrest and agitation which often accompany the attacks are due to an atavistic "flight-complex." The frequency of nocturnal attacks is explained by the reduced oxygen consumption during sleep (tendency to spontaneous anoxemia) and the diminished excitability and tone of the respiratory and vagal centers.

The paroxysms usually terminate favorably, but if fatigue of the respiratory center supervenes, the character of the breathing may be changed to the Cheyne-Stokes variety, respiratory paralysis developing in the most severe cases; and if the failure of the left ventricle is progressive, pulmonary stasis or edema may occur. The therapeutic measures advised are the opiates, morphine in particular, oxygen inhalation, and the nitrites.

A second type of cardiac asthma which is diffeernt from the typical variety is discussed; it is due to pulmonary stasis and is characterized by cyanosis, dyspnea (orthopnea) and hydrops, but is not accompanied by paroxysms of hypertension. Mitral disease with insufficiency of the right ventricle is the usual cause. Venesection, d'gitalis, caffeine, morphia in small doses, and oxygen are indicated, but the prognosis is grave.

There is a good deal of speculation in Wassermann's monograph, but the hypothesis which is offered for the cause of cardiac asthma is attractive and merits further investigation. Inasmuch as the attacks are considered to be the reaction of the central nervous system (medullary centers) to anoxemia, it is surprising that no attempt was made to study the blood gases. B. S.